CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204223Orig1s000

PHARMACOLOGY REVIEW(S)

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 204223
Supporting document/s:	SDN 1, 3, and 8
Applicant's letter date:	May 31, 2012 (SDN 1); July 18, 2012 (SDN 3); and February 7, 2013 (SDN 8)
CDER stamp date:	June 1, 2012 (SDN 1); July 19, 2012 (SDN 3); and February 8, 2013 (SDN 8)
Product:	Morphine Sulfate Injection
Indication:	Opioid agonist for the management of pain not responsive to non-narcotic analgesics
Applicant:	Becton Dickinson and Co.
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, Ph.D.
Supervisor/Team Leader:	R. Daniel Mellon, Ph.D.
Division Director:	Bob A. Rappaport, M.D.
Project Manager:	Christopher M. Hilfiger

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204223 are owned by Becton Dickinson and Co. or are data for which Becton Dickinson and Co. has obtained a written right of reference. Any information or data necessary for approval of NDA 204223 that Becton Dickinson and Co. 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204223.

Reference ID: 3263406

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
1.3 RECOMMENDATIONS 3

2 DRUG INFORMATION 8

2.1 DRUG 8
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 9
2.3 DRUG FORMULATION 10
2.4 COMMENTS ON NOVEL EXCIPIENTS 11
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 11
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 16
2.7 REGULATORY BACKGROUND 16

3 STUDIES SUBMITTED 22

3.1 STUDIES REVIEWED 22
3.2 STUDIES NOT REVIEWED 22
3.3 PREVIOUS REVIEWS REFERENCED 22

4 PHARMACOLOGY 22

4.1 PRIMARY PHARMACOLOGY 22
4.2 SECONDARY PHARMACOLOGY 22
4.3 SAFETY PHARMACOLOGY 22

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 23

5.1 PK/ADME 23
5.2 TOXICOKINETICS 23

6 GENERAL TOXICOLOGY 24

7 GENETIC TOXICOLOGY 24

8 CARCINOGENICITY 25

9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY 25

10 SPECIAL TOXICOLOGY STUDIES 27

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 27

12 APPENDIX/ATTACHMENTS 28

Reference ID: 3263406

1 Executive Summary

1.1 Introduction

The Applicant, Becton Dickinson and Co., is developing a morphine sulfate injection product for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate injection will be available as prefilled syringes containing 2, 4, 5, 8, and 10 mg/mL for IM or IV use. The development program was discussed with the Sponsor via preIND and preNDA meetings completed under preIND 107236. An IND was never formally submitted to the Agency.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical studies submitted in this NDA. There were no novel excipients in the drug product formulation. (b) (4) (Impurity (b) (4) which contains a structural alert for genotoxicity, was detected in the drug substance batch analysis; however, (b) (4) is predicted to be not genotoxic via QSAR analysis and therefore can be regulated as a non-genotoxic impurity. The drug substance and drug product specifications are below the ICH Q3A(R2) and Q3B(R2) qualification thresholds and therefore acceptable. There are no issues with the leachables indentified in the container closure system. In fact, there are no issues with the container closure system as the contain closure system has been used in previously FDA-approved products. The Applicant has submitted osmolality data and their morphine sulfate injection drug product is deemed isotonic. As such, no blood compatibility studies are required. The Applicant is relying up the Agency's previous findings of safety to NDA 202515 (Hospira's Morphine Sulfate injection) and to NDA 19999 (Meridian Medical Technology's Morphine Sulfate injection). The label for the morphine sulfate injection drug product is the same as the label for NDA 202515.

1.3 Recommendations

1.3.1 Approvability

This NDA may be approved from the nonclinical pharmacology and toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Applicant's proposed labeling	*Reviewer's proposed changes*	*Rationale for changes*
INDICATIONS AND USAGE Morphine Sulfate Injection is an	**INDICATIONS AND USAGE** Morphine Sulfate Injection is an	No changes were necessary

Reference ID: 3263406

opioid agonist indicated for the Management of pain not responsive to non-narcotic analgesics. (1)	opioid agonist indicated for the Management of pain not responsive to non-narcotic analgesics. (1)	as the correct Established Pharmacologic Class for morphine was used.
USE IN SPECIFIC POPULATIONS • Pregnancy: Based on animal data, may cause fetal harm. (8.1)	**USE IN SPECIFIC POPULATIONS** • Pregnancy: Based on animal data, may cause fetal harm. (8.1)	No changes were necessary. As per the Maternal Health Team labeling initiative, nonclinical pregnancy information with a reference to Section 8.1 was placed in the Highlights section.
8.1 Pregnancy **Teratogenic Effects** **(Pregnancy Category C)** 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 be given to a pregnant woman only if clearly needed. In humans, the frequency of congenital anomalies have 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. 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. Several literature reports indicate that morphine	**8.1 Pregnancy** **Teratogenic Effects** **(Pregnancy Category C)** No formal studies to access 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. 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. 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. Several literature reports indicate that morphine administered	No changes were necessary to the content. The Applicant's proposed labeling is identical to the current Hospira's Morphine Sulfate Injection (version approved on November 14, 2011) including an introductory paragraph as per the CFR for Category C drugs and human data to be placed first as per the Maternal Heath Team initiative. The Applicant also used a summary of the literature reports describing the effects of morphine on human and animal development. These 2 paragraphs were

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 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 material toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. 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. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.	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 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. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. 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. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.	combined because both addressed the animal developmental and reproductive toxicity of morphine as summarized from the literature.
Nonteratogenic Effects Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been	**Nonteratogenic Effects** Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been	A grammatical error was corrected.

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.	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.	
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, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. 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. Behavioral abnormalities resulting from chronic morphine	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, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis, and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. 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. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals	Grammatical errors were corrected.

Reference ID: 3263406

exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.	included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **Carcinogenesis** Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. **Mutagenesis** No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in these species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*. **Impairment of Fertility** No formal nonclinical studies to	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** Studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. **Mutagenesis** No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*. **Impairment of Fertility** No formal nonclinical studies to	No changes were necessary to the content. The Applicant's proposed labeling is identical to the current Hospira's Morphine Sulfate Injection (version approved on November 14, 2011). The Applicant used a summary of the literature reports describing the effects of morphine on mutagenicity, clastogenicity, and fertility. A grammatical error was

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. 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. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.	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. 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. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, and serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.	corrected.

2 Drug Information

2.1 Drug

CAS Registry Number
6211-15-1

Generic Name
Morphine sulfate

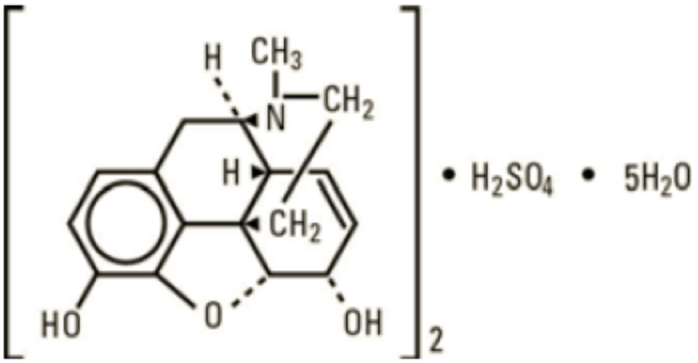
Code Name

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

Reference ID: 3263406

Molecular Formula/Molecular Weight
$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5\ H_2O)$ / 758.83 g/mol

Structure or Biochemical Description



Pharmacologic Class
Opioid agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND#	Drug	Status	Division	Indication	Status Date	Sponsor
107236	Morphine sulfate injection (2, 4, 5, 8, 10 mg/mL)	Presubmission	DAAAP	(b) (4)	11/19/2009	Becton Dickinson and Company

NDA	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
202515	Morphine Sulfate	DAAAP	2, 4, 8, 10, and 15 mg/mL (Injectable)	Approved	November 14, 2011	Management of pain not responsive to non-narcotic analgesics	Hospira, Inc.
19999	Morphine Sulfate Injection (15 mg/mL)	DAAAP	15 mg/mL (Injectable)	Approved	July 12, 1990	Analgesic for intramuscular administration	Meridian Medical Technologies, Inc.

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
(b) (4)	Morphine sulfate USP (b) (4)	(b) (4)	May 8, 2008	(b) (4) was not mutagenic and not clastogenic in genetic toxicity tests (see nonclinical review from November 9, 2010)
(b) (4)	(b) (4)	(b) (4)	November 13, 2001	Deemed adequate to support this NDA for morphine sulfate (see quality review-micro from November 21, 2012) and in a parenteral product (see quality

		(b) (4)		review from August 30, 2012)
			June 20, 1994	Deemed adequate to support a chronic use parenteral product (see quality review from November 8, 2012)
			January 23, 1997	Deemed adequate to support a parenteral product (see quality-micro review from December 13, 2011)
			July 30, 1981	Deemed adequate to support a parenteral product (see quality review from November 7, 2012)
21185	Stabilox canister oxygen absorbing products as manufactured in Buffalo, NY	Multisorb Technologies, Inc.	January 10, 2008	Deemed adequate to support a chronic use parenteral product (see quality review from October 30, 2012)

2.3 Drug Formulation

Morphine Sulfate Injection drug product is formulated in 2, 4, 5, 8, and 10 mg/mL concentrations. The following table illustrates the Morphine Sulfate Injection drug product formulations (adapted from the Applicant's submission):

Ingredient	**Weight (mg per 1 mL) in Formulation**					**MDD of 250 mg (25 mL of the 10 mg/mL formulation)**	**Justified Via FDA-Approved Products**
	2 mg/mL	**4 mg/mL**	**5 mg/mL**	**8 mg/mL**	**10 mg/mL**		
Morphine sulfate	2.0	4.0	5.0	8.0	10.0	250	
Sodium chloride	8.40	8.40	(b) (4)	7.5	7.5	187.5	Yes
Sodium citrate (b) (4)	2.30	2.30		3.45	3.45	86.25	Yes
Citric acid (b) (4)	0.74	0.74		1.11	1.11	27.75	Yes (acute)
Edetate disodium	0.111	0.111		0.111	0.111	2.775	Yes (acute)
Calcium chloride (b) (4)	0.053	0.053		0.053	0.053	1.325	Yes (acute)
Water for injection	Sqf 1 mL	Sqf 1 mL	Sqf 1 mL	Sqf 1 mL	Sqf 1 mL	--	
							(b) (4)
Total weight	1.007 g	1.007 g	1.008 g	1.009 g	1.009 g	--	

The maximum daily dose (MDD) for this drug product is proposed to be 250 mg by the Applicant. The Applicant's proposal of 250 mg as the MDD is acceptable because those patients seeking a higher maximum daily dose would use a higher concentration of morphine sulfate such as from FDA-approved 25 and 50 mg/mL formulations.

As shown in the table above, the daily exposure to each excipient is calculated up to the MDD of 250 mg of morphine sulfate. All the excipients were found in the FDA Inactive Ingredients Guide (IIG) and the Drug Product Reference File (DPRF) in intravenous drug products. Sodium chloride and sodium citrate [redacted] (b) (4) were found in products used chronically and at concentrations of the excipient that were greater than the MDD via this product. Citric acid [redacted] (b) (4), edetate disodium, and calcium chloride [redacted] (b) (4) were found in products used acutely and at concentrations of the excipient that were greater than the MDD via this product.

Citric acid [redacted] (b) (4) is the main organic acid in fruit. Citric acid can be added to foods with no limitations other than current good manufacturing practice as per 21 CFR § 184.1033. The maximum concentration of citric acid in these drug products is 0.111%, which is below the concentration in other FDA-approved IV drug products and therefore does not represent a risk for local tissue toxicity. Further the drug product is intended to be injected into an indwelling catheter line, and therefore will be further diluted prior to reaching the vein. Thus, the systemic citric acid does not represent a safety concern via this drug product.

According to the Hazardous Substances Data Bank (HSDB), an acceptable daily intake for man of edetate disodium is 0 to 2.5 mg/kg. For an average human weighing 60 kg, the maximum acceptable daily intake of edetate disodium is 150 mg. At the MDD, the daily exposure to edetate disodium is [redacted] (b) (4) via this drug product. Thus, edetate disodium does not represent a safety concern via this drug product in terms of systemic toxicity. The maximum concentration in these formulations is 0.0111%, which is lower than that found in other FDA approved IM/IV drug products. There are no safety concerns with this excipient.

The ADI of calcium chloride [redacted] (b) (4) is not limited according to JECFA (http://www.inchem.org/documents/jecfa/jeceval/jec_305.htm). Thus, calcium chloride [redacted] (b) (4) does not represent a systemic safety concern via this drug product. The maximum concentration via these drug products is [redacted] (b) (4)%, which is below that of other FDA-approved IV/IM drug products. Therefore, there are no safety concerns for local tissue toxicity.

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation as all excipients were found in the FDA Inactive Ingredients Guide (IIG) and the Drug Product Reference File (DPRF) at comparable concentrations and total daily doses.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance:
The drug substance specifications are provided in the following table (adapted from the Applicant's submission):

Reference ID: 3263406

Tests	Acceptance Criteria
Residual Solvents	(b) (4)
Related Substances*	
	Total Impurities: NMT (b) (4)%

ND = not detected

The MDD of morphine sulfate via this parenteral formulation is 250 mg/day. According to the ICH Q3A(R2) qualification threshold of a product with a MDD of ≤ 2 g/day is 0.15% or 1 mg/day total daily intake, whichever is lower. The drug substance specifications were set to NMT (b) (4)%. For 250 mg/day of morphine sulfate, the drug substance impurities are 250 mg (b) (4).

Moreover, a review of the genetic toxicity studies (Ames assay and chromosomal aberrations test) done with (b) (4), an (b) (4), is in DMF (b) (4). (b) (4) was found negative in both the Ames assay and the chromosomal aberrations test (see the nonclinical review from November 9, 2010 in DMF (b) (4)).

Impurity (b) (4), which contains a structural alert for genotoxicity, was only present in Lot # 1130049 at (b) (4)%. At the MDD of 250 mg of morphine, (b) (4)% (b) (4) is (b) (4). This exceeds the (b) (4) limit for impurities containing a structural alert for genotoxicity. However, the Applicant submitted a Derek QSAR analysis for (b) (4). There were no Derek alerts for genotoxicity present in (b) (4). The in-house CDER Computational Toxicology Group performed a QSAR analysis for (b) (4) using Derek, Leadscope, (b) (4) also confirmed that (b) (4) is predicted to be negative for genetic toxicity in the Ames assay. The level of (b) (4) in the drug substance is acceptable because (b) (4) is not predicted to be genotoxic by QSAR analysis and it is not present in the drug product batches (see below).

The levels of residual solvents comply with ICH Q3C guidelines. The levels of (b) (4) and (b) (4) in the drug substance specifications are (b) (4), respectively.

The ICH Q3C limitations for (b) (4) and (b) (4) are 3000 and 5000 ppm (3000 ppm = 0.3% and 5000 ppm = 0.5%), respectively.

Therefore, the drug substance specifications and drug substance batch analyses are deemed acceptable.

Drug Product:
The proposed drug product stability specifications are listed below:

Impurity	Specification	Comment
(b) (4)	NMT (b) (4) %	Acceptable as below the ICH Q3B(R2) qualification threshold for nongenotoxic impurities
	NMT %	
	NMT %	
	NMT %	
	NMT %	
	NMT %	
	NMT %	
	NMT %	

According to ICH Q3B(R2), the qualification threshold for drug products with a MDD of >100 mg to 2 g is NMT 0.2% or 3 mg, whichever is lower. The specification for each drug product degradants is NMT (b) (4) %, which is acceptable.

Container Closure System:
The container closure system for the drug product is a single-use prefilled syringe as described in the following table (from the Applicant's submission):

Component	Description (Packaging Configurations)	Supplier	DMF
Primary packaging			
Syringe Assembly	(b) (4)	(b) (4) BD Medical – Pharmaceutical Systems	DMF # (b) (4) BD Medical (syringe (b) (4) DMF # (b) (4) (b) (4)
Plunger Stopper		BD Medical – Pharmaceutical Systems	DMF # (b) (4) and DMF (b) (4) (b) (4)
Plunger Rod		BD Medical – Pharmaceutical Systems	DMF (b) (4) BD Medical
Critical Secondary Packaging			
Oxygen Scavenger Canister	StabilOx® (b) (4) scavenger canister	Multisorb Technologies	DMF (b) (4)
Blister Package ((b) (4)	(b) (4)		N/A
Functional Secondary Packaging			
Blister Package ((b) (4)	(b) (4)		N/A
Carton			N/A

DMFs (b) (4) comprise the primary packaging of the container closure system. DMF (b) (4) was deemed adequate to support this NDA (see quality review-micro dated November 21, 2012) and adequate to support a parenteral product (see quality review dated August 30, 2012). DMF (b) (4) was deemed adequate to support a chronic-use parenteral product (see quality review from November 8, 2012). DMF (b) (4) was deemed adequate to support a parenteral product (see quality review-micro dated December 13, 2011). DMF (b) (4) was deemed adequate to support a parenteral product (see quality review from November 7, 2012). Therefore, the components of the container closure system have been used in FDA-approved parenteral drug products and are not deemed novel.

The primary packaging was examined due to these components having direct contact with the drug product while the secondary packaging would not be in contact with the drug product. Nonetheless, DMF (b) (4) is deemed adequate to support a parenteral product (see quality review dated October 30, 2012).

The Applicant submitted formal extraction testing for the tip cap (b) (4) and the plunger stopper (b) (4), the elastomeric components that come in contact with the drug solutions. Extractable studies were completed using isopropyl alcohol and purified water as solvents. Rubber parts were extracted for 6 hours under reflux conditions. Extraction studies of (b) (4) in water revealed 4 extractables including (b) (4) and 2 unknowns via HS-GC-MS methods. Two unknowns were identified from the (b) (4) elastomer using HS-GC-ME methods along with several organic molecules were found using UPLC/DAD methods, including: (b) (4) and some unknowns.

Leachable data were also provided on 2 and 10 mg/mL lab-scale batches during development. Analyses were performed at initial testing and after 6 months storage at 40°C/75% RH and 25°C/60% RH. The results for the 10 mg/mL solution are presented in the table below (from the Applicant's submission):

Table 81: Leachables studies results on 10mg/mL lab-scale batch

Analytical method	Leachables observed	Specification proposed for Exhibit batches	T0	T6 months			T12 months	
				40°C/75%RH	30°C/65%RH	25°C/60%RH	30°C/65%RH	25°C/60%RH
UPLC/DAD (PPH-WI-223)	N/A	Not more than (b) (4)	All peaks detected (b) (4)	7 unknown peaks are detected. Each peak is (b) (4)	8 unknown peaks are detected. Each peak is (b) (4)	5 unknown peaks are detected. Each peak is (b) (4)	8 unknown peaks are detected. Each peak is (b) (4)	1 unknown peak is detected. Each peak is (b) (4)
HS-GC/MS (PPH-WI-018)	(b) (4) ppb ppm	Complies with USP<467>	(b) (4)	ND	ND	ND	(b) (4)	
	(b) (4) ppb ppm		ND	ND	ND	ND		
	Other peaks		ND	1 unknown peak detected	1 unknown peak detected	1 unknown peak detected	4 unknown peaks detected	5 unknown peaks detected
UPLC/ELSD (PPH-WI-021)	N/A	Not more than (b) (4)	No peak detected	2 unknown peaks are detected. Each peak is (b) (4)	No peak detected	2 unknown peaks are detected. Each peak is (b) (4)	1 unknown peak is detected. Each peak is (b) (4)	1 unknown peak is detected. Each peak is (b) (4)

[1] The percentage and concentration in ppm indicated are an evaluation of quantity of compounds in comparison with the Morphine Sulfate concentration .

As noted in the table, under, long-term, intermediate, and accelerated conditions for 6 and 12 months, there were 2 leachables identified (b) (4) in the batches tested. In the 12-month samples, levels of (b) (4) reached up to (b) (4), which would equate to (b) (4) at the maximum daily dose of 250 mg morphine. This is below the threshold of toxicological concern of 5 mcg/day as proposed by PQRI for parenteral drug products. Likewise, (b) (4) was detected at up to (b) (4), which would equate to (b) (4) at the MDD.

According to the submission, the Applicant originally proposed acceptance criteria for stability of not more than (b) (4) for each single peak of leachable. At the (b) (4) threshold, exposure to a leachable could be as high as (b) (4), which exceeds the PQRI qualification threshold for parenteral products of 5 mcg/day. Based on the

data provided, tightening this specification was deemed feasible to our CMC review team. To meet the PQRI threshold, the Applicant was requested to tighten the specification to NMT (b) (4). The Applicant agreed as illustrated in the table below (from the Applicant's submission):

Test	Acceptance Criteria for Release	Acceptance Criteria in Stability	Analytical Procedure
Leachables	Not Performed for routine release	Each single peak NMT (b) (4)	In-house UPLC/UV screening method [PPH-WI-223]
		Solvent peaks comply with USP <467>	In-house HS-GC-MS for rubber additives [PPH-WI-018]
		Each single peak NMT (b) (4)	In-house UPLC/ELSD (non UV visible) [PPH-WI-021]

Therefore, there are no safety concerns regarding the container closure system as well as the levels of leachables from the container closure system.

2.6 Proposed Clinical Population and Dosing Regimen

The indication of this morphine sulfate injection drug product is for the management of pain not responsive to non-narcotic analgesics. This is considered a chronic indication. According to the Applicant's proposed labeling, the usual starting dose in adults is 0.1 to 0.2 mg/kg every 4 hours as needed for pain management via the IV route or a fixed dose of 10 mg to an average adult weighing 70 kg via the IM route.

2.7 Regulatory Background

The Applicant is submitting this NDA via the 505(b)(2) pathway referencing Hospira's Morphine Sulfate Injection (NDA 202-515).

There were 2 preIND meetings held under PIND 107,236 on May 19, 2010 and March 17, 2011. The following comments were communicated to the Applicant (see meeting minutes from May 19, 2010):

> *Question 7:*
> *BD also believes that based on the current approved products and the medically accepted use of morphine via the proposed routes of administration and at the concentrations proposed, no additional non-clinical studies are required. Does the Agency agree that no non-clinical safety studies will be required?*
>
> **FDA Response:**
> **Yes, the Agency agrees that no new nonclinical studies for morphine sulfate will be required to support the NDA application. However, the NDA application must address the following nonclinical comments:**

Reference ID: 3263406

1. **Impurities**

   Phenanthrene-derivative opioid drug products may contain impurities containing an [redacted] (b) (4) moiety, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to NMT [redacted] (b) (4) or adequate safety qualification must be provided. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.

   For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R2), ICHQ3B(R2)).

   a. **Adequate qualification must include:**

      i. **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.**

      ii. **Repeat dose toxicology of appropriate duration to support the proposed indication.**

   NOTE: Due to the development of tolerance to the effects of opioids, there is no maximum daily dose for these products. This can have a significant impact on the determination of the appropriate qualification thresholds for drug substance and drug product impurities/degradants as per ICH Q3A(R2) and ICH Q3B(R2). The Division will consider the maximum theoretical daily dose for an opioid tolerant individual for your drug product when establishing the safety qualification threshold for impurities, degradants, and the safety of the proposed excipients in your drug product. You should submit clear clinical data to support your proposed maximum theoretically daily dose for this product for review by the Division.

   In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICHQ3A(R2) and Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

Reference ID: 3263406

NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.

2. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. Because you intend to rely upon the Agency's previous finding of safety for an approved product, you must consider the potential need for additional pharmacokinetic data to bridge your product to the referenced product labeling.**

3. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).**

4. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in module 4. Journal articles that are not in English must be translated into English.**

5. **The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).**

   If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product

Reference ID: 3263406

that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion:
The sponsor requested clarification on how to calculate the maximum daily dose for their product in order to establish the safety margin for any impurities, degradents and excipients used in their drug product. The Division recommended that the sponsor gather data on the prescribing practices and use patterns for single-use vial morphine products, which can be used to calculate the maximum daily dose for their product. The Division also advised the sponsor to contact their API manufacturer to determine if their drug substance contains any impurities that may have structural alerts for mutagenicity. The Division acknowledged that it would be acceptable for the sponsor to submit studies that demonstrate comparable impurity and degradant levels between their product and the referenced product; however, the sponsor must ensure that the referenced product storage conditions are comparable to their product. The sponsor should perform this comparison on multiple lots of the referenced product and document the storage conditions for each batch tested. The Division noted that one of the major reasons for an extension of the review clock or a complete response action for NDA submissions is due to issues that result from inadequately qualified impurity levels, requiring the sponsor to conduct and submit genotoxicity studies during the review cycle.

The sponsor requested clarification on the additional pharmacokinetic data needed to bridge the safety of their drug product with the reference product. The Division noted that the exposure margins listed in the non-clinical sections of the labeling for the referenced product are specific for that drug product. The sponsor may need to conduct additional studies, in either humans or animals, in order to demonstrate that the safety margins noted in the referenced label are applicable to their morphine sulfate injection product. The sponsor must demonstrate comparable pharmacokinetics between their product and the referenced drug.

Furthermore, the following comments were also communicated to the Applicant (see meeting minutes from March 17, 2011):

Toxicology

Question 1: As previously mentioned, BD has secured the right to reference Tier 1 (in vitro) genotoxicity studies, which demonstrate that the impurity in question, (b) (4), produced no genotoxic effects in either of the two recognized test systems. A summary of these studies is presented in Attachment III.

Does the Division agree that these studies qualify the impurity to the extent that the thresholds presented in ICH Guidance entitled "Q3A(R2) Impurities in New Drug Substances" can be applied for specification setting purposes?

FDA Response:
The final reports for the Ames assay and the chromosomal aberration assay on (b) (4) may be submitted to characterize the genotoxic potential of this impurity. Final determination of the adequacy of these studies to support the proposed specification will be determined upon review of the final study reports.

No further discussion was needed.

Question 2:
Does the Division agree that no additional studies/qualification work are required in support of the proposed specifications for (b) (4) in the API and finished product?

FDA Response:
As long as, upon review of the data, we concur with your conclusion that the minimal genetic toxicology studies did not demonstrate evidence for genotoxic potential, no further studies would be required to support the proposed drug substance specification of NMT (b) (4) % and the drug product stability specification of NMT (b) (4) %.

No further discussion was needed.

<u>Additional Nonclinical Comments:</u>

1. **We note that you have proposed a drug product specification for (b) (4) of NMT (b) (4) %, which exceeds the ICH Q3B(R2) qualification threshold of NMT 0.2%. To support this proposed specification, the NDA submission must contain adequate safety qualification of (b) (4). 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) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **Repeat dose toxicology of 90-days duration to support the proposed chronic indication.**

2. **We further note that you have identified a drug product degradant, Impurity (b) (4), in your proposed drug product specification. Impurity (b) (4) (b) (4) appears to contain a structural alert for genotoxicity. You must either reduce this impurity to NMT (b) (4), conduct an Ames assay with**

the isolated [redacted] (b) (4) impurity, or provide adequate justification that [redacted] (b) (4) does not possess genotoxic potential.

3. **Moreover, we refer you to the attached list of additional comments for your NDA which also contains additional nonclinical comments that must be adequately addressed in the NDA submission.**

Discussion:
The Sponsor requested clarification on the requirement that [redacted] (b) (4) meet the impurity specification of NMT [redacted] (b) (4)% given that the USP and the European Pharmacopeia (EUSP) specifications are NMT 0.5%, which is higher than the proposed specifications of NMT [redacted] (b) (4)%. The Division stated that the Sponsor must adhere to the impurity specifications outlined in the ICH Q3B(R2) guidance. USP specifications may be based on manufacturing capability rather than toxicology data.

Alternatively, the Sponsor proposed conducting analytical testing on three lots from approved morphine sulfate products to obtain impurity profiles in an effort to demonstrate that the impurity profiles of their product and the approved products are similar. The Division stated that the Sponsor's drug product must meet the Agency's current standard. It is possible that the results of the Sponsor's analytical comparisons may spur the Agency to pursue actions against the approved products, but these analyses would not provide adequate justification for the levels of the [redacted] (b) (4) impurity in the Sponsor's drug product. The Sponsor would still need to adequately qualify the proposed levels of [redacted] (b) (4) by conducting genetic toxicology studies and a repeat-dose toxicology study as outlined in the response. The Division also noted that the standards for impurity levels at the time previous morphine sulfate drug products were approved may not reflect the current standard.

The Division informed the Sponsor that a lack of adequate safety qualification for [redacted] (b) (4) would be considered a review issue that could negatively impact an action on the application, particularly if the Division determines that additional nonclinical studies are needed. In order to comply with the GRMP timeline, the Division may not be able to review data submitted during the review cycle. If the additional data is required to support an approval, this could result in the need for a second review cycle.

The Sponsor requested clarification on the nature of the structural alert found in Impurity [redacted] (b) (4). The Division stated that [redacted] (b) (4) contains an [redacted] (b) (4) [redacted]. Although this has not been recognized as a common structural alert in the past, subsequent to the publication of the Agency's draft guidance on genotoxic and carcinogenic impurities in drug substances and products in 2008, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf, the Agency has been taking a more rigorous

> approach toward identifying structural alters in drug products. The Division advised the Sponsor to conduct an Ames Assay or a quantitative structural-activity relationship (QSAR) analysis to assess the mutagenic potential of (b) (4). A negative result from the QSAR analysis would be confirmed by a similar analysis conducted by the Agency during the review of the Sponsor's NDA submission.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies submitted in this NDA.

3.2 Studies Not Reviewed

There were no nonclinical studies submitted in this NDA.

3.3 Previous Reviews Referenced

A nonclinical review of the genetic toxicity studies (Ames assay and chromosomal aberrations test) performed using morphinine is in DMF (b) (4) (see nonclinical review from November 9, 2010 in DMF (b) (4)).

4 Pharmacology

4.1 Primary Pharmacology

The primary pharmacology of morphine sulfate is obtained from the approved label from Hospira (November, 2011):

> Morphine, a full opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

4.2 Secondary Pharmacology

No new secondary pharmacology data were submitted.

4.3 Safety Pharmacology

Information regarding the effects of morphine sulfate on the Central Nervous System (CNS) is obtained form the approved label from Hospira (November, 2011):

Reference ID: 3263406

> The principle therapeutic action of morphine is analgesia. Other therapeutic effects of morphine include anxiolysis, euphoria and feelings of relaxation. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In common with other opioids, morphine causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Morphine and related opioids depress the cough reflect by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness.

Information regarding the effects of morphine sulfate on the cardiovascular system is obtained from the approved label from Hospira (November, 2011):

> In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine produces peripheral vasodilation which may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics of morphine sulfate is obtained form the approved label from Hospira (November, 2011):

> Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after parenteral administration. Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. A blood-brain barrier exists, and when morphine is introduced outside of the CNS, plasma concentrations of morphine remain higher than the corresponding CSF morphine levels.
>
> Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h in postoperative patients, but shows considerable interindividual variation. The major pathway of clearance is hepatic glucuronidation to morphine-3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10% in the feces. Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours, although the longer half-lives were obtained when morphine levels were monitored over protracted periods with very sensitive radioimmunoassay methods. The accepted elimination half-life in normal subjects is 1.5 to 2 hours.

5.2 Toxicokinetics

There were no toxicity studies using morphine sulfate submitted in this NDA.

Reference ID: 3263406

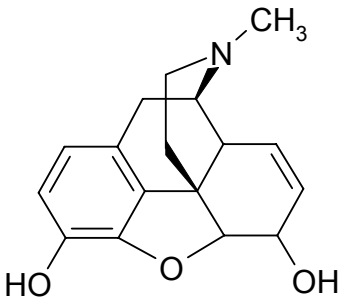
6 General Toxicology

There were no general toxicology studies using morphine sulfate submitted in this NDA.

7 Genetic Toxicology

There were no genetic toxicology studies using morphine sulfate submitted in this NDA.

Opioid products, including morphine, that are derived from thebaine have a process impurity containing a structural alert for mutagenicity described as a [redacted] (b) (4). Compounds containing this structure have been referred to by industry as [redacted] (b) (4). The [redacted] (b) (4) has been demonstrated to be reactive with DNA resulting in genotoxicity and mutagenicity [redacted] (b) (4). Potentially genotoxic compounds present a safety concern, as they could alter the DNA of the cell and could theoretically result in the formation of tumors and cancer. As a result, the agency has maintained that potentially genotoxic substances should be tested for their genotoxic potential or reduced to acceptable levels. One such [redacted] (b) (4). The structure of morphine and the [redacted] (b) (4) impurity are depicted below with the [redacted] (b) (4) circled in red:



Morphine

[redacted] (b) (4)

The genetic toxicity studies (Ames assay and chromosomal aberrations test) on [redacted] (b) (4) were submitted and reviewed in DMF [redacted] (b) (4). [redacted] (b) (4) was found negative in both the Ames assay and the chromosomal aberrations test (see nonclinical review dated November 9, 2010 in DMF [redacted] (b) (4)).

Moreover, the following information regarding the mutagenesis of morphine sulfate is obtained from the approved label from Hospira (November, 2011):

> **Mutagenesis**
> No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest

that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in these species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in *Drosophila*.

8 Carcinogenicity

There were no carcinogenicity studies using morphine sulfate submitted in this NDA. According to the approved label for morphine sulfate from Hospira (November, 2011), studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies using morphine sulfate were not submitted in this NDA.

The following information regarding the teratogenic and nonteratogenic effects of morphine sulfate is obtained from the approved label from Hospira (November, 2011):

8.1 Pregnancy
Teratogenic Effects (Pregnancy Category C)
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 be given to a pregnant woman only if clearly needed.

In humans, the frequency of congenital anomalies have 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. 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.

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 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 material toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed.

Reference ID: 3263406

No maternal toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Nonteratogenic Effects
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 CO2 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.

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

In addition, information on impairment of fertility with morphine sulfate is obtained from the approved label from Hospira (November, 2011):

Impairment of Fertility
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. 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. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

Reference ID: 3263406

10 Special Toxicology Studies

The osmolality of the morphine sulfate products were determined by the Applicant. The following table illustrates the osmolality of the drug product formulations (from the Applicant's submission):

Table 2: Optimization of the quantity of NaCl needed for isotonicity

Strength of Morphine Sulfate Injection solution		2mg/mL	4mg/mL	5mg/mL	8mg/mL	10mg/mL
Osmolality (mOsm/kg) brought by	Morphine Sulfate	7.2	14.4	18.0	28.8	36.0
	Disodium edetate/$CaCl_2$	3.0				
	Citric acid / Sodium citrate	28.0		42.0		
ΔmOsm/kg (rounded) needed to bring solution to 300mOsm/kg		265		235		
Corresponding quantity of NaCl to be added (mg/mL)		**8.4**		**7.5**		
Osmolality measured (mOsm/kg) and batch number		**298** MPH 11-05-168	**304** MPH 11-03-90	**291** MPH 11-04-129	**300** MPH 11-04-130	**306** MPH 11-05-169

In order to simplify the formulae at production sacle, the different formulations were split in two groups (lower strength: 2 and 4 mg/mL and higher strengths: 5, 8 and 10 mg/mL), this permitted to harmonize the quantity of NaCl to add.

As shown in the table above, all of the morphine sulfate formulations are considered isotonic. Ideally, isotonic solutions fall between 275 to 295 mOsm/kg with hypertonic solutions being >350 mOsm/kg. In fact, according to USP <785> Osmolarity and Osmolality, blood osmolality ranges from 285 to 310 mOsm/kg. The morphine sulfate formulations fall with blood osmolality ranges. Since the morphine sulfate formulations are considered isotonic, blood compatibility testing will not be required.

11 Integrated Summary and Safety Evaluation

There were no nonclinical studies submitted in this NDA. There were no novel excipients in the drug product formulation. Drug substance and drug product specifications are below the ICH qualification thresholds and there are no impurities with structural alerts for genotoxicity that have not been adequately qualified. There are no issues with the leachables indentified in the container closure system. In fact, there are no issues with the container closure system as the contain closure system has been used in previously FDA-approved products. The Applicant has submitted osmolality data and their morphine sulfate injection drug product is isotonic. As such, no blood compatibility studies are required. The Applicant is relying up the Agency's previous findings of safety to NDA 202515 (Hospira's Morphine Sulfate injection) and to NDA 19999 (Meridian Medical Technology's Morphine Sulfate injection). The label for the morphine sulfate injection drug product is the same as the label for NDA 202515. From a nonclinical pharmacology and toxicology perspective, this NDA may be approved.

Reference ID: 3263406

12 Appendix/Attachments

References

(b) (4)

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.

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

/s/

CARLIC K HUYNH
02/19/2013

RICHARD D MELLON
02/19/2013
I concur with Dr. Huynh that NDA 204223 may be approved from the nonclinical pharmacology and toxicology perspective.