CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204223Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204223	Submission Date(s): 6-1-2012
Brand Name	Morphine Sulfate Injection, USP
Generic Name	Morphine Sulfate
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Becton, Dickinson & Company
Relevant IND(s)	-
Formulation; Strength(s)	Injection; 2, 4, 5, 8, 10 mg/mL
Indication	Management of pain not responsive to non-narcotic analgesics
Proposed Dosage Regimen	IV or IM every 4 hours. Dose varies.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submission is acceptable from a clinical pharmacology perspective provided that a mutual agreement is reached with regard to the product label.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Becton, Dickinson & Company submitted a 505(b)(2) NDA 204223 for Morphine Sulfate Injection USP use via intravenous and intramuscular injection route for the management of pain. The sponsor would like to rely on Agency's previous findings of safety and efficacy for Morphine Sulfate Injection USP by Hospira NDA 202515 for IV use and Meridian NDA 019999 for IM use.

The Sponsor did not conduct any study with the IV formulation and requested Biowaiver for the proposed IV route of administration. In terms of IM route, the sponsor conducted a relative bioavailability study (MED-11-PREFL01) with the 10 mg/mL strength injection via IM route and the results were included in the submission. The sponsor sought biowaiver for IM use of lower strengths being developed, namely 2, 4, 5, and 8 mg/mL. (b) (4) The sponsor utilized the product labels of Hospira NDA 202515 for IV use and Meridian NDA 019999 for IM use to compose proposed product label.

The relative bioavailability study for the IM formulation is a phase 1, single-center, randomized, open-label, single-dose, 2-period, 2-sequence crossover study in healthy subjects.

					Period 1		Period 2	
Study Day	**-21**	**-1**	**1**		**1**	**2**	**3**	**4**
	Screening Enrollment	Admit to CPC; Naloxone Challenge	R	**Dosing Sequence**	**TRT**		**TRT**	**Study Discharge**
				1	A	W	B	
				2	B	W	A	

Treatment A: Morphine Sulfate United States Pharmacopeia (USP) for injection in a single, 1 mL, IM dose of 10 mg/mL delivered with a BD prefilled syringe administered over 1-2 seconds using a BD Eclipse™ 22G x 1 inch needle, supplied separately.

Strength: 10 mg/mL
Dosage form: IM injection with single-use prefilled syringe
Batch/Lot#: 1251258
Manufacturer: BD Medical (Franklin Lakes, NJ)
Treatment B: A single IM injection from the Meridian morphine auto-injector that dispensed approximately 10 mg of morphine sulfate in a 0.7 mL dose.
Strength: 14.97 mg/mL
Dosage form: IM injection with Meridian morphine auto-injector

Batch/Lot#: 1N3197
Manufacturer: Meridian Medical Technologies, Inc. (Columbia, MD)

The morphine sulfate prefilled syringe was supplied by the sponsor, BD Medical, Franklin Lakes, USA. The Meridian morphine sulfate auto-injector was ordered from Meridian by the sponsor and shipped directly from Meridian to the pharmacy of PRA.

Opioid block was employed with naltrexone (50 mg orally) given 12 hours and 30 minutes before each dose of morphine sulfate and again 12 hours after.

– PK Blood sampling: Blood collections at predose (within 30 minutes prior to dosing); 5, 10, 20, 30, 60 min; 2, 3, 4, 8, 12, 16 hours post dose
– At least 1 day wash out

Table: PK Parameters of Morphine following administration of Meridian and BD IM morphine sulfate injection

Parameter	Statistic	Treatment A (Test) (N=24)	Treatment B (Reference) (N=24)
Cmax (ng/mL)	n	24	24
	Mean	67.40	94.20
	SD	22.519	25.949
	%CV	33.4	27.5
	Median	60.80	93.25
	Min, Max	39.6, 125.0	50.4, 137.0
	Geometric Mean	64.3	90.5
AUC(0-t) (ng*hr/mL)	n	24	24
	Mean	107.926	122.424
	SD	19.0810	23.3090
	%CV	17.7	19.0
	Median	109.617	127.785
	Min, Max	73.00, 143.13	72.48, 157.26
	Geometric Mean	106.2	120.1
AUC(0-inf) (ng*hr/mL)	n	24	24
	Mean	111.3	126.5
	SD	19.32	23.77
	%CV	17.4	18.8
	Median	112.3	131.6
	Min, Max	77, 147	77, 164
	Geometric Mean	109.7	124.2
Tmax (hr)	n	24	24
	Mean	0.1403	0.1368
	SD	0.10215	0.03995
	%CV	72.8	29.2
	Median	0.0833	0.1667
	Min, Max	0.083, 0.500	0.083, 0.167
Lambda_z (1/hr)	n	24	24
	Mean	0.223	0.213
	SD	0.0468	0.0495
	%CV	21.0	23.2
	Median	0.214	0.203
	Min, Max	0.15, 0.37	0.14, 0.36
	Geometric Mean	0.218	0.209
t1/2 (hr)	n	24	24
	Mean	3.230	3.392
	SD	0.5965	0.6672
	%CV	18.5	19.7
	Median	3.236	3.418
	Min, Max	1.87, 4.53	1.93, 4.81

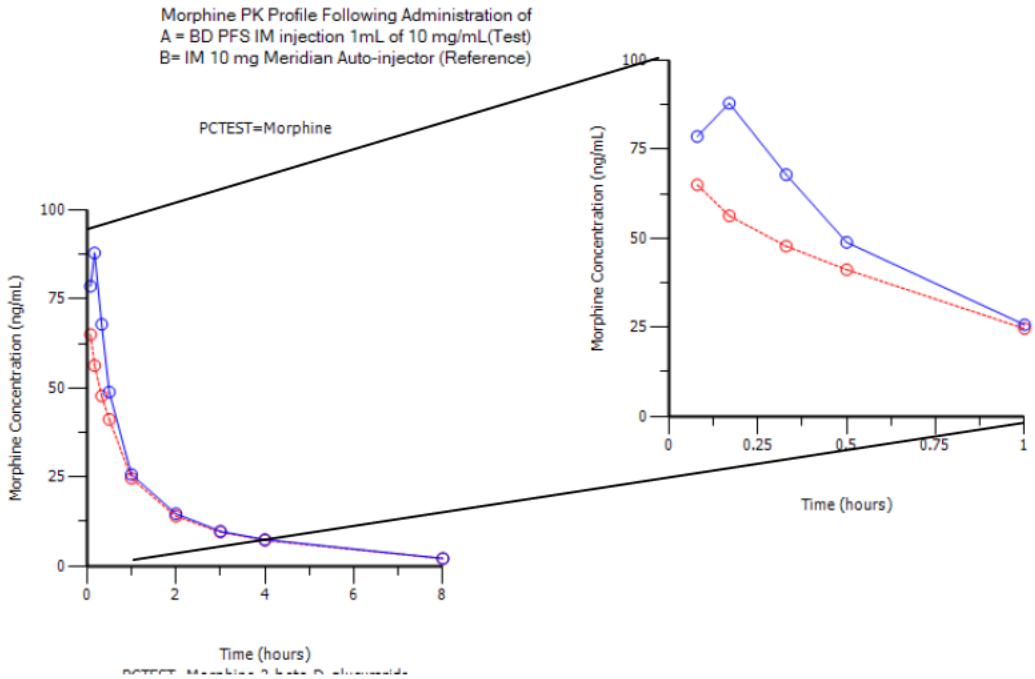
The Meridian morphine auto-injector is nominally a 10-mg product, based on the information in the Meridian labeling. The mean volume dispensed is 0.74 mL and the drug concentration is 15 mg/mL. The actual dose delivered by the Meridian morphine auto-injector is thereby estimated to be closer to (b) (4) mg. The BD prefilled syringe is supplied slightly overfilled and in accordance with clinical practice must be primed prior to use. It was thus anticipated that some dose variability would be introduced by the manual priming process. Therefore, the syringes and auto-injectors were weighed in the PRA pharmacy before and after dosing so that doses delivered in the study could be verified and pharmacokinetic parameters dose normalized appropriately.

Values for Cmax, AUC0-t, and AUC0-∞ were also normalized for the total administered dose, both by dividing by the mean dose or by the actual (exact individual) doses; the results are summarized in the Table below.

Statistical Analysis of Morphine Cmax, AUC0-t, and AUC0-∞ with and without Dose Normalization

Parameter[a]	Geometric LSMean (n=24)		Geometric LSMean Ratio (Trt A/Trt B)		
	BD Prefilled Syringe (Test)	Meridian morphine auto-injector (Reference)	Point Estimate	90% Confidence Interval	
				Lower	Upper
C_{max} (ng/mL)	64.28	90.54	0.710	0.651	0.775
nm[d]-C_{max} (ng/mL)	6.12	8.16	0.751	0.688	0.819
ne[e]-C_{max} (ng/mL)	6.13	8.17	0.750	0.687	0.819
AUC_{0-t} (ng*h/mL)	106.23	120.10	0.885	0.859	0.911
nm-AUC_{0-t} (ng*h/mL)	10.12	10.82	0.935	0.908	0.963
ne-AUC_{0-t} (ng*h/mL)	10.13	10.84	0.934	0.910	0.960
$AUC_{0-\infty}$ (ng*h/mL)	109.65	124.19	0.883	0.859	0.908
nm-$AUC_{0-\infty}$ (ng*h/mL)	10.44	11.19	0.933	0.908	0.960
ne-$AUC_{0-\infty}$ (ng*h/mL)	10.46	11.21	0.933	0.908	0.958

Before dose normalization, the geometric LSMean Cmax for morphine after IM injection with the BD prefilled syringe (Treatment A) was about 71% of the corresponding Cmax after IM injection with the Meridian morphine auto-injector. As shown in Table above, after normalization by either the mean or exact dose, Cmax from Treatment A was about 75% that of Treatment B. The 90% CIs for Cmax were not wholly contained within the 80-125% range for bioequivalence, regardless of dose normalization.



This conclusively indicates that the Cmax of test product or Treatment A (BD prefilled syringe morphine sulfate Injection) is lower than Meridian morphine auto-injector following intramuscular injection. It appears that the BD morphine sulfate IM injection has lower Cmax compared to Meridian's IM injection of morphine sulfate.

1.4 General Biopharmaceutics

BD's proposed product is a parenteral solution intended solely for administration by injection. The composition of the proposed product is similar to the reference product for IV administration, Morphine Sulfate Injection USP by Hospira (NDA 202515) as illustrated in the Table below.

Formulation Comparison of BD's Morphine Sulfate Injection USP and Hospira's Morphine Sulfate Injection USP (IV Reference Product)

Ingredient	Function	BD's Morphine Sulfate Injection USP, 2 mg/mL and 4 mg/mL (Amount per 1 mL Solution)	BD's Morphine Sulfate Injection USP, 5 mg/mL, 8 mg/mL and 10 mg/mL (Amount per 1 mL solution)	Hospira's Morphine sulfate Injection USP, 2 mg/mL, 4 mg/mL, 8 mg/mL and 10 mg/mL (Amount per 1 mL Solution)	Hospira's Morphine Sulfate Injection USP, 15 mg/mL (Amount per 1 mL Solution)
Morphine Sulfate (b) (4)	Active Ingredient	2 mg or 4 mg (as labeled)	(b) (4) 8 mg or 10 mg as labeled)	2 mg, 4 mg, 8 mg or 10 mg (as labeled)	15 mg
Sodium Chloride	(b) (4)	8.40 mg	7.5 mg		(b) (4)

1.5 Analytical

Summary of validation for bioanalytical method employed for analysis of morphine is in the described below. At the request of the Division of Clinical Pharmacology 2, Office of Clinical Pharmacology, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an audit of the clinical and analytical portions of the relative bioavailability study (MED-11-PREFL01). [redacted]^(b) (4)^, an ORA investigator of [redacted]^(b) (4)^, and Dr. Young Moon Choi, a pharmacologist of DBGLPC, participated in the inspection. The inspection team audited all study-related records, including notebooks and source data, and did not observe any objectionable conditions and no Form FDA 483 was issued at the close of the analytical site inspection. Hence, data from the study MED-11-PREFL01 were acceptable for review.

Assay Method Report: PRA-US-0009/ PRALABIN-114547-A

Sample Preparation Technique: Solid-phase extraction

Analytical Technique: Ultra performance liquid chromatography with tandem mass spectrometric detection

Calibration standard concentrations employed:

Morphine: 0.500, 1.00, 2.50, 5.00, 10.0, 20.0, 40.0, and 50.0 ng/mL,
Morphine-3-β-D-glucuronide: 5.00, 10.0, 25.0, 50.0, 100, 200, 400, and 500 ng/mL,
Morphine-6-β-D-glucuronide: 2.00, 4.00,10.0, 20.0, 40.0, 80.0, 160, and 200 ng/mL.

Quality Control Samples:

Analyte	**QC Concentration**		
Morphine	***1.5 ng/mL***	***15 ng/mL***	***40 ng/mL***
Accuracy (bias)	-3.3%	-5.3%	-3.3%
Precision (CV%)	4.3%	12.5%	3.2%
Morphine-3-β-D-glucuronide	***15 ng/mL***	***150 ng/mL***	***400 ng/mL***
Accuracy (bias)	-4%	-4.7%	-2.8%
Precision (CV%)	4.7%	13.6%	3.5%
Morphine-6-β-D-glucuronide	***6 ng/mL***	***60 ng/mL***	***160 ng/mL***
Accuracy (bias)	-2.7%	-4.2%	-1.9%
Precision (CV%)	4%	13.5%	2.7%

Selectivity: All study samples were analyzed in analytical runs for which the blank and zero samples showed co-eluting peaks with responses of no more than 20.0% of the peak response at the lower limit of quantitation (LLOQ) of morphine, morphine-3-β-D-glucuronide and morphine-6-β-D-glucuronide and no more than 5.0% of the peak response of the internal standards.

Dilution of Samples: Study samples were diluted with blank human K^+ EDTA plasma when insufficient sample volume was available or when a concentration was or was

likely going to be obtained above the ULOQ. Accuracy and precision of QC standards after 10X dilution was acceptable.

Maximum undiluted concentration:

Morphine: 400 ng/mL,
Morphine-3-β-D-glucuronide: 4000 ng/mL,
Morphine-6-β-D-glucuronide: 1600 ng/mL
Maximum dilution factor: 10

Incurred Sample Reproducibility: Reproducibility in incurred samples was assessed to show that the method was reliable for samples from dosed subjects. The following procedure was applied:

The total number of samples selected for the assessment of incurred sample reproducibility is 80 for morphine and 60 for morphine-3-β-D-glucuronide and morphine-6-β-D-glucuronide. The concentration of morphine was leading for the selection of samples, spanning the range from peak levels (near Cmax) to low concentrations in the elimination phase (above 3*LLOQ) selected from multiple subjects, with a minimum of two time-points per subject. One determination per sample (in addition to the original analysis, analyzed in a different analytical run than the analytical run used for reporting the original result, analyzed after the original analysis as soon as practically possible). For each reproducibility result, the relative difference from the original result was calculated. For at least 2/3 of the samples, the relative difference had to be within 20.0%. If the criteria were not met, the bioanalysis was put on hold and was continued only after the issue was investigated and resolved. Accuracy and precision of QC standards utilized for incurred sample reproducibility assessment was acceptable.

2 Labeling

Becton, Dickinson and Company intends to market the proposed product in a 1 mL prefilled syringe. The sponsor integrated product labels for IV and IM use based on the following two product labels:

1. The first reference drug is Morphine Sulfate Injection 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL, the subject of NDA 202515, approved on 11/14/2011. The application is held by Hospira. The product is distributed in Carpuject and ISecure syringes.
2. The second reference drug is Morphine Sulfate Injection 15 mg/mL, the subject of NDA 019999, approved 07/12/1990. The application is held by Meridian Medical Technology. The product is distributed in an auto-injector syringe.

The only unique labeling information based on the completed relative bioavailability study is indicated in Clinical Pharmacology Section 12.3 Pharmacokinetics. The sponsor proposed text is indicated in regular font, reviewer recommendation is indicated as bold font or strikethrough text for additions and deletions, respectively.

(b) (4)

Average peak morphine plasma levels of 67.4 ± 22.5 ng/mL were noted around 5 to 30 minutes following intramuscular injection of 10 mg morphine sulfate from a prefilled syringe.

In addition, the following paragraph is added.

(b) (4)

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SRIKANTH C NALLANI
01/23/2013

YUN XU
01/24/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204223	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	June 1, 2012		
Division:	Division of Anesthesia, Analgesia and Addition Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Becton Dickinson (BD) Medical	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	June 18, 2012
Established Name:	Morphine Sulfate Injection, USP	**Date of Review:**	January 2, 2013
Indication:	For the management of pain not responsive to non-narcotic analgesics	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Dosage form/ strengths	Solution for Injection/ 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, 10 mg/mL		
Route of Administration	IV or IM injection		
Type of Review:	Biowaiver Request		

SUBMISSION:

The proposed drug product is a sterile solution for injection intended to be administered via the intravenous (IV) or intramuscular (IM) route of administration. The proposed drug product is packaged in a pre-filled single-use disposable syringe containing 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, or 10 mg/mL morphine sulfate as the active ingredient. This application is an electronic NDA, filed as a 505(b)(2) application, with Hospira's morphine sulfate injection (NDA 202515) as the IV reference listed drugs (RLD) and Meridian Medical Technology's morphine sulfate injection (NDA 19999) as the IM RLD.

BIOPHARMACEUTICS INFORMATION:

The Applicant is requesting a waiver of the requirement to provide evidence of in-vivo bioavailability for the IV route of administration. In support of the IM route of administration, the Applicant has performed a comparative in vivo bioavailability study of the 10 mg/mL strength of the proposed drug versus Meridian's 15 mg/mL morphine sulfate injection IM reference product (this study will be reviewed by the Clinical Pharmacology reviewer from OCP). The Applicant was asked (IR dated 11/1/12) to submit a Biowaiver request to support the use of the lower strengths by IM administration. This review is focused on the evaluation of the two Biowaiver requests (for the IV and the IM routes of administration).

BIOWAIVER REQUEST FOR THE IV ROUTE OF ADMINISTRATION:

The Applicant is requesting a waiver of the requirement to provide evidence of in-vivo bioavailability for the IV route of administration of the proposed morphine sulfate injection drug product as allowed under 21 CFR 320.22(b)(1). The Applicant claims that:

- Morphine sulfate injection is a parenteral drug product intended solely for administration by injection
- The composition of the proposed drug product is similar to the IV RLD by Hospira (NDA 202515).

ASSESSMENT OF THE BIOWAIVER REQUEST FOR THE IV ROUTE OF ADMINISTRATION:

The compositions for the formulations of the proposed BD drug product and the IV RLD product (Hospira) are as follows:

Table 1: Formulation Comparison of BD's Morphine Sulfate Injection USP and Hospira's Morphine Sulfate Injection USP (IV Reference Product)

Ingredient	Function	BD's Morphine Sulfate Injection USP, 2 mg/mL and 4 mg/mL (Amount per 1 mL Solution)	BD's Morphine Sulfate Injection USP, 5 mg/mL, 8 mg/mL and 10 mg/mL (Amount per 1 mL solution)	Hospira's Morphine sulfate Injection USP, 2 mg/mL, 4 mg/mL, 8 mg/mL and 10 mg/mL (Amount per 1 mL Solution)	Hospira's Morphine Sulfate Injection USP, 15 mg/mL (Amount per 1 mL Solution)
Morphine Sulfate (b) (4)	Active Ingredient	2 mg or 4 mg (as labeled)	(b) (4) 8 mg or 10 mg as labeled)	2 mg, 4 mg, 8 mg or 10 mg (as labeled)	15 mg
Sodium Chloride	(b) (4)	8.40 mg	7.5 mg	(b) (4)	
Sodium Citrate (b) (4)		2.30 mg	3.45 mg	-	-
Citric Acid (b) (4)		0.74 mg	1.11 mg	0.4 mg	0.8 mg
Edetate Disodium		0.111 mg t	0.111 mg t	0.2 mg	0.2 mg
Calcium Chloride Dihydrate		0.053 mg	0.053 mg	-	-
Sodium Hydroxide	pH adjuster	-	-	As needed to adjust pH to 2.5 – 4.0	As needed to adjust pH to 2.5 – 4.0
Hydrochloric Acid	pH adjuster	-	-	As needed to adjust pH to 2.5 – 4.0	As needed to adjust pH to 2.5 – 4.0
Water for Injection	Solvent	Sqf 1mL	Sqf 1 mL	Sqf 1 mL	Sqf 1 mL

Sqf = Sufficient quantity for t Present in the proposed formulation as the (b) (4)

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The difference between the proposed drug product and the IV RLD are:

1) The proposed drug product contains an additional ingredient, sodium citrate (b) (4), intended to serve as a (b) (4).
2) The proposed drug product does not contain the pH adjusting agents, sodium hydroxide and hydrochloric acid
3) The proposed drug product contains a small amount of calcium chloride (b) (4) (b) (4).
4) The pH range for the proposed drug product is (b) (4) whereas the pH range for the IV RLD is 2.5-4.0.

Considering the fact that morphine sulfate has a good solubility in water ((b) (4) at room temperature), the above differences will not affect the bioavailability of this drug product when administered by the IV route. Therefore, we consider that the in vivo BA/BE of the proposed morphine sulfate injection administered by the IV route is self-evident, and the Applicant's request for a Biowaiver for their proposed morphine sulfate injection product administered by the IV route is acceptable and the Biowaiver is granted.

BIOWAIVER REQUEST FOR THE IM ROUTE OF ADMINISTRATION:

The Applicant was asked (IR dated 11/1/12) to submit a Biowaiver request to support the use of the lower strengths by IM administration:

Your label indicates that all proposed strengths of your proposed drug product will be intended for IM (and IV) administration. However, you have conducted the comparative BA/BE study for the IM route of administration using only the 10 mg/mL strength of your drug product. Please submit a request to waive the BA/BE study requirement for the IM administration of the lower strengths of your drug product along with an appropriate justification. Include a table comparing the compositions of the drug products with different strengths and a rational of why any difference in the compositions will or will not have an impact on the bioavailability of the lower strength drug products as compared to the 10 mg/mL drug product after IM administration.

The Applicant has responded in an amendment dated 11/20/12 as follows:
BD Rx's request for waiver of the requirement to provide evidence of in-vivo bioavailability of the lower strengths of its product for IM administration is supported by the provision in 21 CFR 320.22(b)(1). The compositions of the proposed lower strengths of BD Rx's product are (b) (4) to the composition of BD Rx's proposed 10 mg/mL strength, for which evidence of in-vivo bioavailability has been demonstrated, as

illustrated in the table below. Although the composition of the lower strengths is qualitatively different than the composition of the IM reference product by Meridian, the in-vivo study performed by BD Rx on its 10 mg/mL product versus the Meridian product demonstrated that these differences do not impact systemic morphine exposure.

Ingredient	Function	BDRx's Morphine Sulfate Injection USP, 2 mg/mL and 4 mg/mL (Amount per 1 mL Solution)	BDRx's Morphine Sulfate Injection USP, 5 mg/mL, 8 mg/mL and **10 mg/mL** (Amount per 1 mL solution)	Meridian's Morphine sulfate Injection USP, 15 mg/mL (Amount per 1 mL Solution)[3]
Morphine Sulfate (b) (4)	Active Ingredient	2 mg or 4 mg (as labeled)	(b) (4) 8 mg or 10 mg as labeled)	15 mg (labeled as 10 mg/0.7 mL)
Sodium Chloride	(b) (4)	8.40 mg	7.5 mg	-
Sodium Citrate (b) (4)		2.30 mg	3.45 mg	-
Citric Acid (b) (4)		0.74 mg	1.11 mg	-
Edetate Disodium		0.111 mg ŧ	0.111 mg ŧ	1 mg
Calcium Chloride (b) (4)		0.053 mg	0.053 mg	-
Benzyl Alcohol		-	-	15 mg
Sodium Hydroxide	pH adjuster	-	-	-
Hydrochloric Acid	pH adjuster	-	-	-

ASSESSMENT OF THE BIOWAIVER REQUEST FOR THE IM ROUTE OF ADMINISTRATION:

The qualitative compositions of all strengths of the proposed drug product are (b) (4). The quantitative differences between the lower strengths (2 mg/mL, 4 mg/mL, 5 mg/mL, and 8 mg/mL) of the proposed drug product and the 10 mg/mL strengths of the proposed drug product are:

1) The 2 mg/mL and 4 mg/mL strengths of the proposed drug product contains 8.40 mg/mL sodium chloride compared to 7.5 mg/mL sodium chloride for the (b) (4), 8 mg/mL, and 10 mg/mL strengths of the proposed drug product.
2) The 2 mg/mL and 4 mg/mL strengths of the proposed drug product contains 2.30 mg/mL sodium citrate (b) (4) compared to 3.45 mg/mL sodium citrate (b) (4) for the (b) (4)

(b) (4) 8 mg/mL, and 10 mg/mL strengths of the proposed drug product.

3) The 2 mg/mL and 4 mg/mL strengths of the proposed drug product contains 0.74 mg/mL citric acid (b) (4) compared to 1.11 mg/mL citric acid (b) (4) for the (b) (4) (b) (4) 8 mg/mL, and 10 mg/mL strengths of the proposed drug product.
4) All strengths of the proposed drug product contain the same amount of edetate disodium (EDTA) and calcium chloride (b) (4). Therefore the ratio of EDTA and calcium chloride (b) (4) to the drug substance is different for each strength of the proposed drug product.

The small difference in the amount of (b) (4) sodium chloride, is not expected to affect the bioavailability of morphine via the IM route of administration, (b) (4) and it does not react with the drug substance, morphine. The (b) (4) sodium citrate (b) (4) and citric acid (b) (4), are added to the proposed drug product to maintain the pH of the drug product solution at pH (b) (4) and are not expected to interact with the drug substance, and are not expected to impact the bioavailability or solubility of the drug substance, morphine. The drug substance has a pKa of 7.9. EDTA is added to the proposed drug product (b) (4) and calcium chloride (b) (4) he difference in the ratio of EDTA and calcium chloride (b) (4) to the drug substance is not expected to impact the drug substance bioavailability or solubility. It should be noted that morphine sulfate has a good solubility in water (b) (4) at room temperature). The Applicant has conducted a comparative BA/BE study for the IM route of administration using the highest strength (10 mg/mL) of the proposed drug product. A waiver of the requirement to provide evidence of in-vivo bioavailability of the lower strengths of the proposed drug product for IM administration is granted based on the comparison between the formulations, and considering the functions and expected lack of effect of the differences in excipient concentrations in the proposed drug product on the bioavailability and solubility of the drug substance.

RECOMMENDATION:

A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study for the IV route of administration (for all strengths) is granted based on the formulation comparison of the proposed drug product and Hospira's morphine sulfate injection (the IV reference product). A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study for the lower strengths (2 mg/mL, 4 mg/mL, 5 mg/mL, and 8 mg/mL) using the IM route of administration is also granted, based on the formulation comparison of these lower strengths and the 10 mg/mL strength. From the Biopharmaceutics perspective, NDA 204223 for Morphine Sulfate Injection (2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, and 10 mg/mL) is recommended for APPROVAL.

Signature
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
John Duan, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
01/02/2013

JOHN Z DUAN
01/02/2013