CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW
Memorandum

NDA: 202515	Submission Date: 1/14/11
Submission Type; Code:	Original; 505(b)(2);
Brand/Code Name:	To be determined
Generic Name:	Morphine Sulfate Injection, USP
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Yun Xu, Ph.D.
OCP Division:	DCP2
OND Division:	Division of Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Hospira, Inc.
Relevant IND(s):	-
Formulation; Strength(s):	• 2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml of morphine sulfate packaged in a Carpuject™ with Luer Lock or iSecure™ Prefilled syringe (b) (4) [redacted]
Proposed Indication:	Management of pain in patients where an opioid analgesic is appropriate.

Recommendation

The Office of Clinical Pharmacology has reviewed the submission dated January 14th, 2011 and finds it acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling.

Labeling recommendation

The following labeling recommendation is proposed:

~~**12 CLINICAL PHARMACOLOGY**~~
~~**12.1 Mechanism of Action**~~
(b) (4) [redacted]

~~**12.2 Pharmacodynamics**~~

~~**12.3 Pharmacokinetics**~~

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine, a pure 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.

Effects on the Central Nervous System (CNS)
The principal 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 reflex by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle
Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result may be constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System
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.
Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

12.2 Pharmacodynamics
Morphine concentrations are not predictive of analgesic response, especially in patients previously treated with opioids. The minimum effective concentration varies

widely and is influenced by a variety of factors, including the extent of previous opioid use, age and general medical condition. Effective doses in tolerant patients may be significantly higher than in opioid-naïve patients.

12.3 Pharmacokinetics

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.

Discussion

Hospira, Inc. submitted a New Drug Application (NDA) for Morphine Sulfate Injection USP in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The reference products for intravenous and intramuscular routes in this submission are Duramorph®, NDA 18565, and Morphine Sulfate Injection (in auto-injection system), (b) (4) The indication and route of administration are the same as prescribed and recommended for the use of the listed drugs. The proposed drug product is a sterile aqueous solution. The Applicant has been marketing this product without an approved NDA.

The Applicant submitted published literature information to support the non-clinical requirements (Dr. Elizabeth Bolan's review, 6/17/11). (b) (4) Additionally, no clinical studies were conducted with the proposed product.

No clinical pharmacology studies were conducted with the proposed product. The Applicant requested a biowaiver of the in vivo study requirements for (b) (4) intravenous (b) (4) based on 21CFR320.22. The biowaiver request was reviewed by ONDQA Biopharmaceutics team and concluded that the sponsor's biowaiver request for intravenous route is acceptable (b) (4) (Dr. Minerva Hughes' review, 6/30/2011).

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/s/

DAVID J LEE
10/20/2011

YUN XU
10/20/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-515	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	14 January 2011		
Division:	Division of Anesthesia and Analgesia Products	**Team Lead:** Angelica Dorantes, Ph.D.	
Sponsor:	Hospira	**Supervisor:** Patrick Marroum, Ph.D.	
Trade Name:	None proposed	**Date Assigned:**	2 February 2011
Generic Name:	Morphine Sulfate Injection, USP	**Date of Review:**	30 June 2011
Indication:	Pain not responsive to nonnarcotic analgesics	**Type of Submission:** Original NDA – 505 (b)(2)	
Formulation/strengths	2 , 4 , 8, 10, 15 (b) (4) mg/mL		
Route of Administration	IV (b) (4)		
Type of Review:	**Biowaiver Request**		

SUBMISSION: NDA 202-515 was submitted by Hospira in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of Morphine Sulfate Injection USP in the treatment of pain not responsive to nonnarcotic analgesics. Morphine sulfate is an opiate agonist that has been used in clinical practice for the treatment of pain since the 1800's. This NDA was submitted in an effort to achieve compliance with FDA's position that all marketed drugs should have an approved marketing application, *FDA guidance on Marketing Unapproved Drugs – Compliance Policy Guide (2006)*. Hospira holds other approved marketing applications for morphine sulfate injection (NDA 19916: 0.5 – 5 mg/mL, IV-patient controlled, ANDA 071849, and ANDA 071850); however, the approved dosage strength and presentations are different in comparison with this new NDA. (b) (4)

BIOPHARMACEUTICS INFORMATION:

A waiver of the CFR's requirement to provide data from in vivo bioavailability or bioequivalence studies to support the approval of Morphine Sulfate Injection was requested on the basis that the product is an injectable solution and its bioavailability is self-evident, as per 21 CFR §320.22 *(Criteria for waiver of evidence of in vivo bioavailability or bioequivalence)*.

In support of the requested biowaiver for Morphine Sulfate Injection, NDA 202-515 included the following information for review and evaluation:

- Formulation comparison table which included composition data for approved products
- Literature references for bioavailability and pharmacokinetic performance

The biopharmaceutics data are summarized and reviewed in the attached Reviewer's Notes section of this report.

CONCLUSION/RECOMMENDATION:

A waiver of the CFR's requirement to provide vivo bioavailability or bioequivalence data is granted for Morphine Sulfate Injection administered by the intravenous route (b) (4)

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Patrick Marroum, Ph.D.
Biopharmaceutics Supervisor, ONDQA

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REVIEWER'S NOTES

BIOPHARMACEUTICS REVIEW

Morphine Sulfate Injection USP is formulated as a sterile solution containing morphine sulfate and the inactive ingredients edetate disodium, citric acid, and sodium chloride. Hydrochloric acid or sodium hydroxide may be added for pH adjustment. The product is supplied in pre-filled syringes, (b) (4) .

The applicant's request for a biowaiver was based on the following:

(1) § 320.22(b)(1)(i) – Parenteral solution intended for administration by injection

A. Proposed drug product labeling:

(b) (4)

B. **Reviewer's Comments:** The proposed labeling indicates that the product is a parenteral solution intended for administration by injection, (b) (4) intravenous (IV) (b) (4) Based on this information, the criterion for a waiver based on §320.22(b)(1)(i) is met. Of note, the regulation does not distinguish between the different routes of injection and the mechanism of parenteral drug delivery can affect bioavailability. Data supporting equivalence to approved products are summarized and reviewed in following sections.

(2) § 320.22(b)(1)(ii) – Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved NDA or ANDA

A. Formulation Comparison Table (Approved products vs. NDA 202-515) in NDA

	NDA 18565 Approval – 1984	**NDA 19999 Approval - 1990**	**Pending Submission**
Applicant	Baxter Healthcare	Meridian Medical	Hospira
Indication	Pain not responsive to nonnarcotic analgesics	Pain	Pain not responsive to non narcotic analgesics
Strength(s)	0.5, 1, 10, 25 mg/mL	15 mg/mL	2, 4, 8, 10, 15, (b) (4) mg/mL
Inactive Ingredients	Per 1 mL (Syringe) NaCl – 9 mg Per mL (Infusion)	Per 1 mL (*Vol = 0.7 mL*) Benzyl alcohol – 15 mg EDTA – 1 mg H_2SO_4 – q.s. for pH	Per 1 mL (syringe) EDTA – 0.2 mg Citric acid – 0.4 mg NaCl – (b) (4)

	NDA 18565 Approval – 1984	**NDA 19999 Approval - 1990**	**Pending Submission**
Applicant	Baxter Healthcare	Meridian Medical	Hospira
	NaCl – 6.25 – 8 mg $NaOH/H_2SO_4$ – q.s. for pH Final pH = 2.5-6.5	Final pH 2.5 – 6.0	HCl/NaOH – q.s. for pH <u>Per 1 mL (vials)</u> EDTA – 0.2 mg Citric acid – (b) (4) NaCl – (b) (4) HCl/NaOH– q.s. for pH Final pH = 2.5 (b) (4)
Route of Administration	*0.5 and 1 mg/mL*: IV, epidural, and intrathecal injection *10 and 25 mg/mL*: intrathecal and epidural only using a micro infusion device	IM (*vastas muscle*)	*2, 4, 8, 10, 15 mg/mL*: IV (b) (4) (Not for intrathecal or epidural)
Dosage Form	DOSETTE ampoules 10 mL – 0.5 and 1 mg/mL 20 mL – 10 and 25 mg/mL	Auto-injector 10.5 mg/0.7 mL (doses 10 mg, 5% overage)	(b) (4)
RLD (Generic Rx)	Yes	Yes	-

RLD= reference listed drug.

B. **Reviewer's Comments:** The NDA provided a summary table comparing the proposed morphine sulfate injection product to approved reference listed drugs (RLD). The excipients citric acid and HCl were not used in the RLDs, but these excipients were approved for use at the same concentration in other approved Hospira morphine sulfate injection products. The excipient EDTA was also used at a lower concentration in the proposed drug product compared with approved morphine products, 0.2% compared with 1%. EDTA was used as an (b) (4) in the proposed formulation. It is an approved excipient in other injection products for (b) (4) IV, (b) (4) Concentration differences for inactive ingredients permitted by the regulations (§314.127(a)(8)(ii)(B)) for parental products referencing an RLD are changes in preservatives, buffers, and antioxidants that do not affect the safety and efficacy of the product. The inactive ingredients meet this criteria and the different EDTA concentration for the proposed product is not expected to affect its bioavailability, and thus, safety and efficacy, when used as intended. Therefore, bioavailability differences for this morphine sulfate injection product will depend on the route of delivery and concentration of active.

Assessment of Formulation for Intravenous Injection

Morphine sulfate is an old drug with numerous published reports on its pharmacokinetic and analgesic properties (>100 cited in NDA). Its use in pain management is accepted medical practice and dosing guidelines are outlined in standard medical reference books for oral, IV, intrathecal, epidural, subcutaneous and IM administration. No clinical or biopharmaceutic studies were submitted to NDA 202515. Reference was made to NDA 18565 (approved IV product) and published clinical studies as the basis for submission (i.e., 505(b)2).

Morphine sulfate is a highly water soluble compound, and, as stated previously, the proposed formulation does not contain any additives expected to affect the rate and extent of systemic exposure. The applicant has proposed IV products ranging from (b) (4) to 15 mg/mL. From

a bioavailability perspective, a bolus or infused IV injection provides the drug directly to the intravascular space, regardless of the volume of delivery. No absorption is involved and bioavailability may be considered self-evident. In clinical practice, morphine sulfate is administered on a mg/kg basis (refer to Prescribing Information) and not based on volume, with an initial IV dose of 2 – 10 mg/70 kg adult. The IV morphine RLD provides for a 0.5 mg/mL and 1 mg/mL morphine solution for direct IV injection; however, the total dose delivered using the approved product is expected to be within the range of concentrations proposed by this applicant (i.e., 2 – 15 mg). Additionally, the applicant's morphine injection products were within the range of the referenced RLD's morphine injection for intrathecal and epidural administration using a microinfusion device (i.e., Infumorph at 10 mg/mL and 25 mg/mL). This concentration morphine injection product is not diluted before infusion and intrathecal delivery is thought to have systemic exposures similar to IV delivery. Thus, a means to bridge safety and efficacy for all proposed concentrations could be discerned. The suitability of a biowaiver for the different morphine injection products was discussed further with the clinical team (Dr. Sharon Hertz, Dr. Ellen Fields, and Dr. Timothy Jiang). Additional in-use data were requested from the applicant and reviewed by the clinical reviewer (T. Jiang). From the clinical team's perspective, a bolus IV injection of morphine up to 15 mg/mL does not raise any new safety concerns and all products currently provide a benefit the public.

In consideration of the route of administration, dosing procedures, formulation, and clinical feedback, a waiver of bioavailability/bioequivalence studies is granted for the intravenous route of administration.

(b) (4)

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/s/

MINERVA HUGHES
06/30/2011

PATRICK J MARROUM
06/30/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**202515**	**Brand Name**	**Morphine sulfate Injection, USP**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	
Medical Division	**DAAP**	**Drug Class**	**Opioid analgesic**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Management of pain in patients where an opioid analgesic is appropriate.**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Solution 2, 4, 8, 10, 15, (b) (4) mg/mL**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**Jan 14, 2011**	**Route of Administration**	**IV (b) (4) Injection**
Estimated Due Date of OCP Review	**Oct 10, 2011**	**Sponsor**	**Hospira**
Medical Division Due Date	**Oct 17, 2011**	**Priority Classification**	**Standard**
PDUFA Due Date	**Nov 14, 2011**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				**Sponsor requests a biowaiver.**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**This application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, so sponsor believes the requirement of 21CFR314.55 do not apply.**
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	No clinical study was conducted with the proposed product.
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		Sponsor requests a biowaiver.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			x	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	This application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, so sponsor believes the requirement of 21CFR314.55 do not apply.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and			x	

	biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Hospira, Inc. submited a New Drug Application (NDA) for Morphine Sulfate Injection USP in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The basis for this submission is Duramorph®, NDA 018565, and Morphine Sulfate Injection (in auto-injection system), (b) (4) The indication and route of administration are the same as prescribed and recommended for the use of the RLD. The proposed drug product is a sterile aqueous solution.

Sponsor requests a waiver of the in vivo study requirements based on 21CFR320.22. This biowaiver request will be reviewed by ONDQA. Since this application is not for a new active ingredient, new indication, new dosage form, new dosing regiment, or new route of administration, sponsor believe the requirements of 21CFR314.55 with regards to pediatric use information do not apply.

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/s/

DAVID J LEE
03/10/2011

YUN XU
03/10/2011

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202515	**Reviewer:** Minerva Hughes, PhD	
Submission Date:	14 January 2011		
Division:	Division of Anesthesia, Analgesia, and Rheumatology Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Hospira	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	None proposed	**Date Assigned:**	2 February 2011
Generic Name:	Morphine Sulfate Injection, USP	**Date of Review:**	01 March 2011
Indication:	Pain not responsive to nonnarcotic analgesics	**Type of Submission:** Original NDA – 505 (b)2 Biowaiver Request	
Formulation/strengths	Injection, Solution: 2 mg/mL; 4 mg/mL; 8 mg/mL; 10 mg/mL; 15 mg/mL; (b) (4)		
Route of Administration	Intravenous (b) (4)		

SUBMISSION: NDA 202-515 was submitted by Hospira in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the use of morphine sulfate injection, USP in the treatment of pain not responsive to nonnarcotic analgesics. The NDA was submitted in an effort to achieve compliance with FDA's position that all marketed drugs should have an approved marketing application, *FDA guidance on Marketing Unapproved Drugs – Compliance Policy Guide*. Hospira currently holds approved marketing applications for morphine sulfate; however, the formulation strength and presentations are different in comparison with this new submission. In addition, this NDA is for (b) (4) intravenous injection routes. The applicant requests a waiver for bioavailability/bioequivalence studies on the basis that the requirements of 21 CFR 320.33 are met. That is, the drug product is:

1. a parenteral solution intended solely for administration by injection
2. contains the same active and inactive ingredients in the same concentration as an approved drug product

BIOPHARMACEUTIC INFORMATION: In support of the requested biowaiver, NDA 202-515 includes the following supportive biopharmaceutics data for review and evaluation:

- Proposed drug product composition and dosage form
- Formulation comparison table which includes composition data for approved products
- Literature references for bioavailability and pharmacokinetic performance

RECOMMENDATION:
From a biopharmaceutics perspective, the application is recommended for filling. The suitability of the waiver request will be a review issue.

Minerva Hughes
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick Marroum
Biopharmaceutics Team Leader or Supervisor
Office of New Drugs Quality Assessment

cc: Angelica Dorantes, Ying Wang, Kimberly Compton, Swati Patwardhan

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MINERVA HUGHES
03/01/2011

PATRICK J MARROUM
03/02/2011