CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202515/000	**Sponsor:**	HOSPIRA INC
Code:	170		275 NORTH FIELD DR DEPT 0389 BLDG H2 2
Priority:	7		LAKE FOREST, IL 60045
Stamp Date:	14-JAN-2011	**Brand Name:**	MORPHINE SULFATE
PDUFA Date:	14-NOV-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	15-SEP-2011	**Product Number; Dosage Form; Ingredient; Strengths**	

001; INJECTABLE; MORPHINE SULFATE; 2MG
002; INJECTABLE; MORPHINE SULFATE; 4MG
003; INJECTABLE; MORPHINE SULFATE; 8MG
004; INJECTABLE; MORPHINE SULFATE; 10MG
005; INJECTABLE; MORPHINE SULFATE; 15MG
(b) (4)

FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	Y. WANG	Review Chemist		301-796-1479
	D. CHRISTODOULOU	Team Leader		301-796-1342

Overall Recommendation:	ACCEPTABLE	on 10-NOV-2011	by D. SMITH	()	
	WITHHOLD	on 27-JUL-2011	by C. CRUZ	(HFD-323)	301-796-3254

Establishment:	**CFN:** 1925262	**FEI:** 1925262	
	HOSPIRA WORLDWIDE, INC 1776 CENTENNIAL DR MCPHERSON, KS 674609301		
Duns:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	(b) (4) SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-FEB-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** 3004591926	
	HOSPIRA WORLDWIDE, INC 375 N FIELD DRIVE LAKE FOREST, IL 60045		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-FEB-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER (b) (4)		
Profile:		**OAI Status:**	NONE
Milestone:	OC RECOMMENDATION		
Milestone Date:	10-FEB-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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/s/

NIKOO N MANOCHEHRI KALANTARI
11/22/2011

Addendum to CMC Secondary Review Revising Recommendation (to Approval)

From: Ying Wang
To: NDA 202515
Through: Prasad Peri
Date: November 10, 2011

Subject: Withdrawal of [redacted] (b) (4) manufacturing site and change in status of the overall compliance issued Nov. 10, 2011.

The manufacturing site at Hospira [redacted] (b) (4) has on-going cGMP deficiencies that have not been resolved as of this writing. The Office of Compliance issued a withhold recommendation for this site as well as for the NDA 202515 on July 27, 2011. This site is responsible for the manufacturing of drug product [redacted] (b) (4) Per discussion with the Agency on Nov. 9, 2011 in a teleconference, the applicant withdrew the [redacted] (b) (4) site as well as the [redacted] (b) (4) presentation of the drug product from NDA 202515 on November 9, 2011. This action removed cGMP deficiencies from this NDA. The remaining sites in the NDA have acceptable cGMP status. Note that the drug product presentations in Isecure™ and Carpuject™ are currently manufactured in the McPherson, Kansas, facility which has an acceptable cGMP status. The Office of Compliance issued an overall acceptable recommendation for the revised NDA on November 10, 2011. This NDA is therefore recommended for approval from CMC perspective.

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/s/

YING WANG
11/10/2011

PRASAD PERI
11/10/2011
I concur

NDA 202515

Morphine Sulfate (IV and IM) Injection, USP.
Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Hospira Inc.
275 North Field Dr.,
Lake Forest, IL 60064

Indication: For the management of pain not responsive to non-narcotic analgesics

Dose

- The usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed to control the pain. The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size.
- The usual starting dose for continuous infusion is 0.1 mg to 5 mg per incremental dose. The dose should be adjusted depending on the severity of pain and patient's response and tolerance. Maximal dosing rates up to 30 mg/h (3 mg every 6 minutes) are common for opioid tolerant patients. (2.1)
- (b) (4)
- Applicant's maximum daily dose is 722 mg/day.

Presentations:

- Morphine Sulfate Injection USP, 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, and 15 mg/mL, is available in single-use CarpujectTM and iSecure™ syringes for intravenous administration.
- (b) (4)
- (b) (4)

EER Status:	Recommendations:	Withhold
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Not recommended
	DMETS-	Acceptable

Biopharm–	Acceptable
Microbiology –	Adequate
Pharm/toxicology –	Adequate

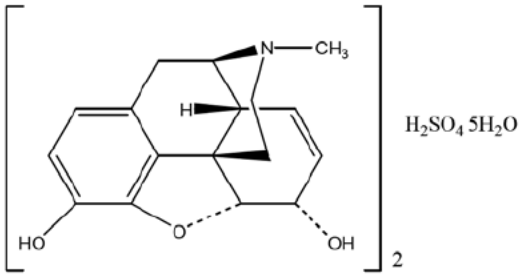
Original Submission: 14-Jan-2011

Post-Approval CMC Agreements: None

Background:
This is a standard NDA with a 10 month clock. The NDA is in electronic format with labeling provided in SPL format. In response to the FDA 2006 guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide," Hospira, Inc. has filed an NDA for their morphine sulfate Product (505(b)(2) application) that references literature and the Agency's previous findings of efficacy and safety for Duramorph (NDA 18,565) by Baxter Healthcare for the IV injection, (b) (4)

Drug Substance:
Morphine is the most important alkaloid of opium and is a phenanthrene derivative. It is chemically designated as 7,8-Didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3,6-diol sulfate (2:1) (salt), pentahydrate, having the following structural formula

Figure 1. Chemical Structure



Molecular Formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

Molecular Weight: 758.83

Morphine Sulfate USP is a fine, white powder. When exposed to air it gradually loses water of hydration, and darkens on prolonged exposure to light. It is soluble in water and ethanol at room temperature.

The drug substance is manufactured in (b) (4) and all information is referenced in DMF (b) (4). Specifications that are provided in the NDA for the drug substance mostly follow the USP monograph. Additional specifications for related substances meet ICH Q3A guidance. The drug substance is controlled by testing for Identity (IR, Color, sulfate), Specific Rotation, Acidity, Water Content, Residue on Ignition, (b) (4), Residual Solvents, Assay, related Substances, Aerobic Microbial Count, and Bacterial Endotoxins.

Morphine sulfate is packaged in [redacted] (b) (4)

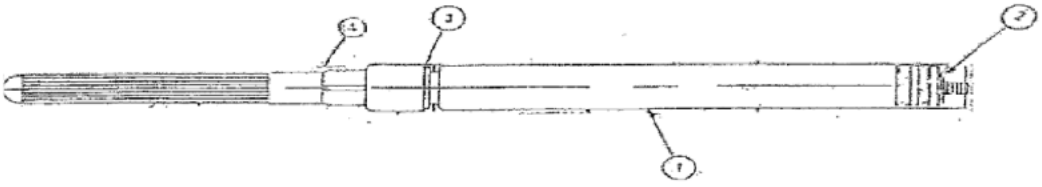
Hospira has assigned a minimum retest period of [redacted] (b) (4).

Conclusion: The drug substance is satisfactory.

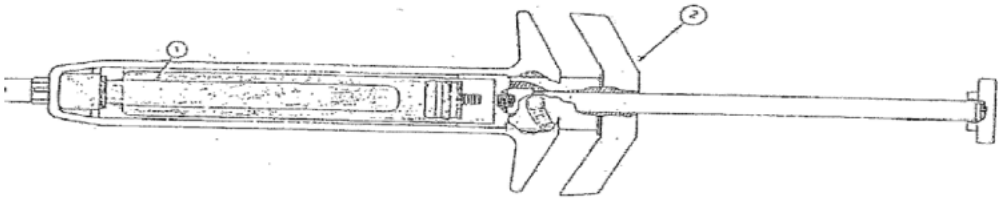
Drug Product:
The drug product Morphine Sulfate Injection USP is a sterile aqueous solution. There are [redacted] (b) (4) configurations of the container closure system and [redacted] (b) (4) concentrations of the drug product in this application. The drug product is an unapproved but currently marketed product in the US. The drug product is light sensitive and needs to be protected from the light during storage. The drug product specification mostly follows the USP monograph with additional acceptance criteria for related substances. The acceptance criteria for pH, Edetate Disodium and total impurities have been tightened during the review cycle based on the pharmaceutical development study results and batch stability data.

Diagram of iSecure™ Syringe

Prefilled Syringe



1 Glass Cartridge
2 Plunger
3 (b) (4) Seal
4 Needle Assembly



1 Prefilled Syringe (non-activated)
2 Carpuject® Holder

Representative formulations Qualitative and Quantitative compositions are provided below.

Component	Drug Code Number (Computer#) [1]	Quality Standard	Function
Morphine Sulfate (b) (4)	(b) (4)	USP, Ph.Eur	Active Ingredient
Edetate Disodium (b) (4)		USP	(b) (4)
Citric Acid (b) (4)		USP	
Sodium Chloride		USP	Tonicity
Hydrochloric Acid		NF	pH adjustment
Sodium Hydroxide		NF	pH adjustment
Water for Injection		USP, Ph.Eur	Vehicle
(b) (4)			

Table 2. Quantitative Composition – Morphine Sulfate Injection USP, 2 mg/mL, 1 mL in 2 mL Carpuject® and 1 mL in 1 mL iSecure™

Component	Quantity per Milliliter (mL)	Strength: 2 mg/mL
		2 mg/1 mL
		Quantity per Unit
Morphine Sulfate USP (b) (4)	2.00 mg	2 mg
Edetate Disodium USP (b) (4)	0.20 mg	0.2 mg
Citric Acid USP (b) (4)	0.40 mg	0.4 mg
Sodium Chloride USP	(b) (4)	(b) (4)
Hydrochloric Acid NF (1N)		
Sodium Hydroxide NF (1N)		
Water for Injection USP		q.s. to fill volume
(b) (4)		
Total Volume	1.00 mL	1 mL

[1] The final pH range of the finished drug product is 2.5 – (b) (4)

(b) (4)

Table 2. Hospira Formulations

Morphine Sulfate (mg/mL)	Edetate Disodium (mg/mL)	Citric Acid (mg/mL)	Sodium Chloride (mg/mL)	HCl / NaOH	(b) (4)	Product Configuration
(b) (4)						
15	0.2	0.8	(b) (4)	q.s. to pH	(b) (4)	Carpuject® iSecure™
10	0.2	0.4		q.s. to pH		Carpuject® iSecure™
8	0.2	0.4		q.s. to pH		Carpuject® iSecure™
4	0.2	0.4		q.s. to pH		Carpuject® iSecure™
2	0.2	0.4		q.s. to pH		Carpuject® iSecure™

The drug product is manufactured by Hospira in McPherson, KS (b) (4). The McPherson, Kansas site manufactures the Carpuject® syringes and iSecure™ syringes. (b) (4)

(b) (4)

The container closure system for Morphine Sulfate Injection USP in Carpuject® prefilled syringe consists of four (4) components: glass cartridge, plunger, (b) (4) seal (cap) with rubber liner, and needle assembly. The components used in the primary packaging of the subject drug product, along with the source of supply, are identified in Table 1. While integral to drug delivery, the needle assembly component is not considered a primary packaging component, as it does not have direct contact with the solution.

Based on the stability data generated for Morphine Sulfate Injection USP registration stability batches, Hospira proposes that the expiration dating be set at twenty four (24) months for all presentations of the subject drug product, when stored at controlled room temperature (20 – 25°C; 68 – 77°F).

Conclusion: The drug product is acceptable.

CMC issues that are still pending:
An acceptable recommendation from the Office of Compliance.

Office of Compliance deficiency
Drug product manufacturing and testing sites will need to have acceptable compliance status prior to an approval.

Overall Conclusion: The NDA is recommended for **Complete Response** from CMC standpoint.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

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/s/

PRASAD PERI
10/17/2011
CR due to Compliance issues.

NDA 202515

Morphine Sulfate Injection, USP

Hospira

Ying Wang, PhD

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment III
Branch VIII

CMC REVIEW OF NDA 202515
For the Division of Anesthesia, Analgesia and Addition Products
(HFD-170)

Table of Contents

CMC Review Data Sheet

1. NDA 202515

2. REVIEW #: 1

3. REVIEW DATE: 30-Spet-2011

4. REVIEWER: Ying Wang, PhD

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	Jan. 14, 2011
Correspondence (C)	
Amendment (BC)	July 12, 2011
Amendment (BC)	Aug. 22, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc.
Address:	275 North Field Dr., Lake Forest, IL 60064
Representative:	Melissa A. Nguyen
Telephone:	620-241-6200 Ext. 6315

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Morphine Sulfate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 7
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Opioid Analgesic

11. DOSAGE FORM: Injectable

CMC Review Data Sheet

12. STRENGTH/POTENCY: 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, (b) (4)

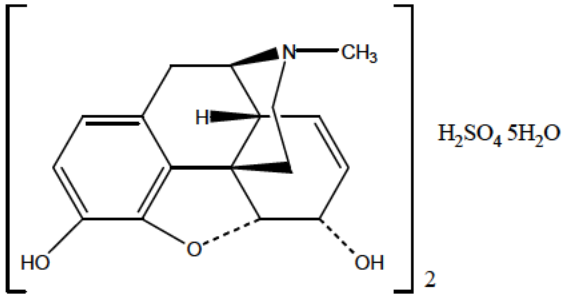
13. ROUTE OF ADMINISTRATION: Intravenous (b) (4)

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Abstracts Service (CAS) Index Name	Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5alpha, 6alpha)-, sulfate (2:1) salt, pentahydrate
CAS Registry Number	6211-15-0
United States Adopted Name (USAN)	Morphine Sulfate
International Nonproprietary Name (INN)	Morphine Sulfate
Molecular Structure	
Molecular Formula	$(C_{17}H_{19}NO_3)_2 \bullet H_2SO4 \bullet 5H_2O$
Molecular Weight	758.83

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	Oct. 7, 2005	
	III			3	Adequate	April 10, 2007	
	III			3	Adequate	March 7, 2008	
	II			3	Adequate	July 11, 2011	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	July 27, 2011	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Bio waiver for IV is granted. (b) (4)	June 30, 2011	Minerva Hughes, PhD
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	See comments in review	Sept 15, 2011	Mathilda Fienkeng
EA	Categorical exclusion claim is acceptable	May 12, 2011	Raanan Bloom
Microbiology	Approvable pending resolution of micro labeling issue	Sept. 23, 2011	Bryan S. Riley, PhD

The CMC Review for NDA 202515

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time, all CMC review deficiencies have been resolved.
However, this NDA is recommended for complete response action due to the overall WITHHOLD recommendation from the Office of Compliance.

The proposed expiry of twenty-four (24) months for all presentations of the drug product when stored at controlled room temperature (20 – 25°C; 68 – 77°F) is granted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance Morphine Sulfate USP is a fine, white powder. When exposed to air it gradually loses water of hydration, and darkens on prolonged exposure to light. It is soluble in water and ethanol at room temperature. Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. Specifications that are provided in the NDA for the drug substance mostly follow the USP monograph. Additional specifications for related substances meet ICH Q3A guidance.

(2) Drug Product

The drug product Morphine Sulfate Injection USP is a sterile aqueous solution. There are (b) (4) configurations of the container closure system and (b) (4) concentrations of the drug product in this application. The drug product is an unapproved but currently marketed product in the US. The drug product is light sensitive and needs to be protected from the light during storage. The drug product specification mostly follows the USP monograph with additional acceptance criteria for related substances. The acceptance criteria for pH, Edetate Disodium and total impurities have been tightened during the review cycle based on the pharmaceutical development study results and batch stability data.

Stability data for 12 month long term storage condition (25°C/40% RH) and 6 month accelerated storage condition (40°C/<20% RH) are provided in the submission. The stability data support the proposed expiry of twenty-four (24) months for all presentations of the drug product when stored at controlled room temperature (20 – 25°C; 68 – 77°F).

B. Description of How the Drug Product is Intended to be Used

Morphine Sulfate Injection USP, when packaged in Carpuject® or iSecure™ syringe, is intended for single use intravenous [redacted] (b) (4) administration. It is available in concentration of 2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml, and 15 mg/ml. [redacted] (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

One of the drug product manufacturing sites, Hospira [redacted] (b) (4) has been recommended for withhold by the Office of Compliance due to the GMP compliance issues. The entire site is on OAI alert. The Office of Compliance issued an overall WITHHOLD recommendation for this NDA on July 27, 2011.

Prior to approval of this NDA an overall acceptable recommendation from the Office of Compliance is required.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Ying Wang, PhD

B. Endorsement Block:

(See appended electronic signature page)

Prasad Peri, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

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/s/

YING WANG
10/05/2011

DANAE D CHRISTODOULOU
10/05/2011
For Prasad Peri

Initial Quality Assessment
Office of New Drug Quality Assessment
Division III, Branch VIII
Division of Anesthesia, Analgesia and Addiction Products

OND Division:	Anesthesia, Analgesia and Addiction
NDA:	202515
Chemical Classification	3S
Applicant:	Hospira
Stamp date:	January 14, 2011
PDUFA Date:	October 14, 2011
Trademark:	NA
Established Name:	Morphine sulfate, USP Injection
Dosage Form:	Injection, 2 mg/ml; 4 mg/ml; 8 mg/ml; 10 mg/ml; 15 mg/ml; (b) (4)
Route of Administration:	Parenteral (IV, (b) (4)
Indication:	Treatment of acute pain
CMC Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is submitted as a 505(b)(2), based on the approved NDAs 18-565, Duramorph® (morphine sulfate injection), help by Baxter. (b) (4) The proposed formulation, is a marketed unapproved product, by Hospira. A comparison to the referenced approved products is provided by the applicant:

Table 1. Comparison of the Hospira morphine sulfate injection to the referenced drugs

	Reference Listed Drug	Reference Listed Drug	Generic Equivalent
	Baxter Healthcare DURAMORPH®	(b) (4)	**Hospira, Inc. Morphine Sulfate Injection USP**
Conditions of Use	Management of pain not responsive to non-narcotic analgesics		Management of pain not responsive to non-narcotic analgesics
Active Ingredient	Morphine Sulfate		Morphine Sulfate
Inactive Ingredients[1]	Each milliliter contains Sodium Chloride 9 mg in Water for Injection.		Each milliliter contains Edetate Disodium 0.2 mg in Water for Injection. Each milliliter also contains Citric Acid 0.4 mg for the 2 mg, 4 mg, 8 mg, and 10 mg Morphine Sulfate or Citric Acid 0.8 mg for the 15 mg, 25 mg and 50 mg Morphine Sulfate. Sodium Chloride is also added to adjust isotonicity. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust pH.
Route of Administration	Injection (Intravenous/epidural/ intrathecal)[2]		Injection (Intravenous/Intramuscular)[3]
Dosage Form	Injectable		Injectable
Strength	0.5 mg/mL and 1 mg/mL		2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, 25 mg/mL and 50 mg/mL

1 Refer to Section 3.2.P.2 *Pharmaceutical Development.*

2 Epidural and intrathecal routes of administration are not applicable for the subject drug product. Refer to Section 1.14.1 *Hospira proposed product labeling.*

(b) (4)

The Hospira product contains edetate disodium outside (b) (4) range than the referenced drug. The application is filed based upon the applicant's request for a waiver of *in vivo* bioequivalence or bioavailability studies, as per 21 CFR 320.22. A pre-NDA meeting/agreements has been conducted with the Agency on 12/08/2009.

The proposed drug product will be available in the strengths and configurations shown in Table 2, below. Note that the Carpuject™ and iSecure™ syringes (reference 510k #K063180, iSecure™ Syringe Cartridge Assembly, decision date 12/11/06) were reviewed recently in NDA 200-403 (hydromorphone HCl injection), also held by Hospira. These are manual injection systems and not autoinjectors. In

(b) (4)

Table 2. Proposed strengths and configurations for the Hospira product

NDC Number	Strength (Total Morphine Content)	Fill Volume	Container Size and Type	Proposed Manufacturing Site
0409-1890-01	2 mg/mL (2 mg)	1 mL	2 mL Carpuject® Syringe	Hospira, McPherson, KS
0409-1891-01	4 mg/mL (4 mg)	1 mL	2 mL Carpuject® Syringe	
0409-1892-01	8 mg/mL (8 mg)	1 mL	2 mL Carpuject® Syringe	
0409-1893-01	10 mg/mL (10 mg)	1 mL	2 mL Carpuject® Syringe	
0409-1894-01	15 mg/mL (15 mg)	1 mL	2 mL Carpuject® Syringe	
0409-1890-11	2 mg/mL (2 mg)	1 mL	1 mL iSecure™ Syringe	
0409-1891-11	4 mg/mL (4 mg)	1 mL	1 mL iSecure™ Syringe	
0409-1892-11	8 mg/mL (8 mg)	1 mL	1 mL iSecure™ Syringe	
0409-1893-11	10 mg/mL (10 mg)	1 mL	1 mL iSecure™ Syringe	
0409-1894-11	15 mg/mL (15 mg)	1 mL	1 mL iSecure™ Syringe	

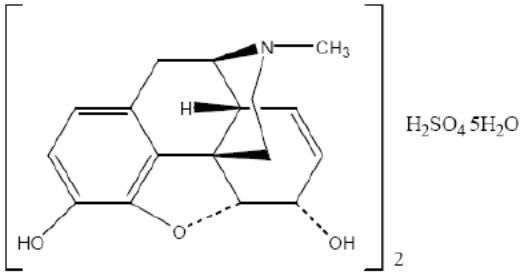
(b) (4)

B. Review, Comments and Recommendations

Drug Substance Hydromorphone HCl

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Chemical Name(s): 7, 8-didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1) (salt), pentahydrate (IUPAC);
Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) salt, pentahydrate (CAS)
Molecular formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$
Molecular weight: 758.83
CAS: 6211-15-0



$H_2SO_4\,5H_2O$

The drug substance is manufactured by (b) (4), and referenced to DMF (b) (4). LoA is included in the NDA. DMF (b) (4) has been reviewed previously and deemed adequate in the latest review of 1/24/2010, by Nashed Samaan. The applicant provided a list of potential impurities in the NDA, which were identified by names and chemical structures, see below. Specifications of impurities that contain a structural alert for mutagenicity, e.g., (b) (4) should be assessed in consultation with the Toxicology Division.

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

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF (b) (4) should be assessed. An information request has been sent to the DMF holder regarding impurities specifications by the latest reviewer.
2. Suitability of the drug product manufacturing process, which includes (b) (4), should be assessed in consultation with the Microbiology division. In addition, in-process controls, microbiolgical integrity of the closures, and process validation should be assessed.
3. (b) (4) from manufacturing conditions and the finished product, should be assessed.
4. The drug product contains NaCl as a tonicity agent. Osmolality/isotonicity of the drug product should be assessed.
5. The specification for the end-product pH range of 2.5 – (b) (4) should be compared with the target pH during manufacture and evaluated upon review.
6. Compatibility of the drug product with common diluents used for IV infusion.
7. Specifications for drug product impurities/degradants as per ICHQ3B(R) in consultation with the Toxicology Division.
8. Adequacy of the information provided for extractables, suitability and compatibility of the packaging system, including the leachables/extractables evaluation should be assessed in consultation with the Toxicology division.
9. Regulatory status of the iSyringe™ cartridge system (b) (4)

10. Proposed expiration dating of 24 months, including storage orientations, conditions of storage and adequacy of the NDA batches as representative data for all proposed commercial configurations.
11. Photostability data as per ICH Q1B. The drug product is claimed to be protected from light by the secondary packaging.
12. Labeling in SPL format.

D. **Comment for the 74-day Letter**:

1. Provide an updated summary for the primary stability batches included in the NDA. In addition, provide updated stability data in inverted configurations, e.g., vials, Carpuject® and iSyringe™ cartridges.

E. **Recommendation for fileability**: The NDA is fileable based on sufficient number of primary stability batches, and 12- month real time stability data at 25°C/40% RH and a biowaiver request to the approved products. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is recommended for team review with a biopharmaceutics reviewer for evaluation of the biowaiver to the referenced products. The drug substance is not an NME, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development.

Consults:

1. Microbiology (requested)
2. Biopharmaceutics, ONDQA (requested; reviewer: Minerva Hughes)
3. Toxicology (to be determined and initiated by the primary reviewer)

Danae D. Christodoulou, Ph.D. 1/29/2011
CMC Lead Date

Prasad Peri, Ph.D. _____
Acting Branch VIII Chief, ONDQA Date

NDA Number: 202515 **Supplement Number and Type: 3S** **Established/Proper Name: Morphine sulfate injection**

Applicant: Hospira **Letter Date: 01/14/2011** **Stamp Date: 01/14/2011**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		(b) (4) DMF (b) (4)
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Injectable drug product

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)		7/16/2010	API
	3			9/16/2009	(b) (4)
	3			1/14/2010	
	3			1/14/2010	
	3			1/14/2010	
	3			8/11/2010	
	3			2/2/2010	
	3			2/2/2010	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**			Based on sufficient body of data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	X		
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See above

{See appended electronic signature page}

Name of
PAL: Danae Christodoulou 1/29/11 Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief (Acting): Prasad Peri Date
Division of Pre-Marketing Assessment III
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/

DANAE D CHRISTODOULOU
04/05/2011
Initial Quality Assessment

PRASAD PERI
04/05/2011
I concur