CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202515	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (none) Established/Proper Name: morphine sulfate injection, USP Dosage Form: Injection Strengths: 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, 15 mg/mL, (b) (4)		
Applicant: Hospira Inc.		
Date of Receipt: January 14, 2011		
PDUFA Goal Date: 11-14-11	Action Goal Date (if different): 11-12-11	
Proposed Indication(s): management of pain not responsive to non-narcotic analgesics		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Duramorph	Reproductive toxicology data: NOTE: Sponsor appears to have used language from the Duramorph label; however, these data are actually based on literature references.
Literature	Pharmacology, nonclinical ADME, genetic toxicology, reproductive and developmental toxicology

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor requested a waiver from *in vivo* BA/BE requirements which was granted because the proposed product is an injectable solution and its bioavailability is self-evident, as per 21 CFR 320.22. In support of the biowaiver, the sponsor submitted a formulation comparison table which included composition data for approved products, and literature references for bioavailability and pharmacokinetic performance.
The waiver was granted only for studies comparing the proposed product to the IV product relied-upon, NDA 18565 Duramorph, (morphine sulfate) Injection (Baxter).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐
*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒
*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Duramorph (morphine sulfate injection, USP) 0.5 mg/mL, and 1.0 mg/mL	N 018565	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for the addition of new strengths and configurations for morphine sulfate. Previously approved morphine sulfate injection could only be administered via a pump, however this product can be given intravenously.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

NDA#	022321	Embeda (morphine sulfate and naltrexone hydrochloride) Extended-Release Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg.
NDA#	021260	Avinza (morphine sulfate extended-release) 30 mg, 45, mg, 60 mg, 75 mg, 90 mg, and 120 mg Capsules
NDA#	020616	Kadian (morphine sulfate extended-release) 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg Capsules
NDA#	021671	DepoDur (morphine sulfate extended-release liposome injection)
NDA#	018565	Duramorph PF (morphine sulfate injection, USP), 0.5 mg/mL and 1.0 mg/mL
NDA#	019916	Morphine sulfate injection 1 mg/mL
NDA#	019999	Morphine sulfate injection
NDA#	201517	Morphine sulfate oral solution 20 mg/mL
NDA#	022195	Morphine sulfate oral solution
NDA#	019977	Oramorph SR (morphine sulfate sustained release) Tablets, 15 mg, 30 mg, 60 mg, and 100 mg.
NDA#	022207	Morphine sulfate IR tablets
ANDA#	Various	Generic Extended-Release tablets and injectables

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

KIMBERLY A COMPTON
11/14/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	November 10, 2011
Reviewer(s):	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Morphine Sulfate Injection, USP 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL
Application Type/Number:	NDA 202515
Applicant:	Hospira
OSE RCM #:	2011-214-1

1 INTRODUCTION

This memo summarizes DMEPA's evaluation of the revised proposed container labels and carton labeling submitted by Hospira November 7, 2011. These revisions were made in response to comments DMEPA provided in OSE Review # 2011-212 on October 7, 2011. Additionally, the single-use (b) (4) previously included with this application were withdrawn by Hospira on November 9, 2011.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 7, 2011
- Carton Labeling submitted November 7, 2011
- Insert Labeling submitted November 9, 2011

Additionally, DMEPA reviewed the comments provided to Hospira in OSE review # 2011-212 regarding the Carpuject and isecure syringes.

3 RESULTS AND DISCUSSION

The proposed use of color on the Morphine Sulfate Carpuject labels and labeling draws the eye to the drug name rather than the product strength. The use of color field to differentiate strengths should include the strength presentation. All the strengths are presented as white font on a black field or background which makes them appear more similar and thus less differentiated.

This proposed use of color and black may be used for the differentiation of a single strength (e.g. 2 mg/mL) but not all the strength presentations. Additionally, printing white font over a gray field may be difficult to read on the small Carpuject label. Thus, the proposed presentation is acceptable for the Carpuject 2 mg/mL strength.

The proposed isecure container labels and carton labeling include our recommendations and are acceptable from a medication error perspective.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed Carpuject labels and labeling introduce vulnerability that can lead to medication errors because the strengths are inadequately differentiated. We recommend the following:

A. Container Label- Carpujects (All strengths but 2mg/mL)

The use of the same black field behind all the strength presentations lacks adequate differentiation. The use of color as proposed draws the eye to the drug name rather than the product strength. Delete the black field behind the strength presentation. Revise and extend the color field used for the drug

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

name to include the strength. We recommend you leave the 2 mg/mL strength as proposed.

B. Carton Labeling- Carpujects (All strengths but 2mg/mL)

See Comment A.

If the Division has further questions or need clarifications, please contact Danyal Chaudry, project manager, at 301-796-3813.

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

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

/s/

RICHARD A ABATE
11/10/2011

CAROL A HOLQUIST
11/14/2011

PMR/PMC Development Template

NDA 202515

PMR/PMC Description: Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	04/30/2012
	Final Report Submission:	07/31/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The current drug product specification for (b) (4) exceeds the ICH Q3B(R2) safety qualification threshold of NMT 0.2%. Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since the drug product is already a marketed product and this drug product impurity has been previously reported as a morphine degradant in the literature. However, definitive safety qualification data do not exist. Should the required study demonstrate positive potential for mutagenicity, the specification will be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. Knowledge regarding the genotoxic potential for a compound is used to establish safe specifications and ensure drug product quality. The goal of the study is to evaluate the genotoxic (mutagenic) potential of (b) (4).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vitro genetic toxicology study.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 202515

PMR/PMC Description: Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug product impurity [redacted] (b) (4), tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	04/30/2012
	Final Report Submission:	07/31/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The current drug product specification for [redacted] (b) (4) exceeds the ICH Q3B(R2) safety qualification threshold of NMT 0.2 Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since the drug product is already a marketed product and this drug product impurity has been previously reported as a morphine degradant in the literature. However, definitive safety qualification data do not exist. Should the required study demonstrate positive potential for mutagenicity, the specification will be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. Knowledge regarding the genotoxic potential for a compound is used to establish safe specifications and ensure drug product quality. The goal of the study is to evaluate the genotoxic (mutagenic) potential of [redacted] (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vitro genetic toxicology study.

Required

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☐ Registry studies
☐ Primary safety study or clinical trial
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Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 202515

PMR/PMC Description: Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity (b) (4), tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	04/30/2012
	Final Report Submission:	07/31/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The current drug product specification for (b) (4) exceeds the ICH Q3B(R2) safety qualification threshold of NMT 0.2%. Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since the drug product is already a marketed product and this drug product impurity has been previously reported as a morphine degradant in the literature. However, definitive safety qualification data do not exist. Should the required study demonstrate positive potential for clastogenicity, the specification will be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. Knowledge regarding the genotoxic potential for a compound is used to establish safe specifications and ensure drug product quality. The goal of the study is to evaluate the genotoxic (clastogenic) potential of (b) (4).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vitro genetic toxicology study using mammalian cells.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials

☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 202515

PMR/PMC Description: Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug product impurity [redacted] (b) (4), tested up to the limit dose for the assay.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	04/30/2012
	Final Report Submission:	07/31/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The current drug product specification for [redacted] (b) (4) exceeds the ICH Q3B(R2) safety qualification threshold of NMT 0.2%. Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since the drug product is already a marketed product and this drug product impurity has been previously reported as a morphine degradant in the literature. However, definitive safety qualification data do not exist. Should the required study demonstrate positive potential for clastogenicity, the specification will be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Genetic toxicology studies are conducted to ascertain the potential for a compound to interact with and damage DNA. DNA damage is believed to contribute to the potential for carcinogenicity. Knowledge regarding the genotoxic potential for a compound is used to establish safe specifications and ensure drug product quality. The goal of the study is to evaluate the genotoxic (clastogenic) potential of [redacted] (b) (4).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vitro genetic toxicology study using mammalian cells.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 202515

PMR/PMC Description: Conduct a 3-month repeat-dose toxicology study in a single species with the following drug product impurities: (b) (4)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	06/30/2012
	Final Report Submission:	10/31/2012
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

The current drug product specifications for (b) (4) exceed the ICH Q3B(R2) safety qualification threshold of NMT 0.2%. Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since the drug product is already a marketed product and these drug product impurities have been previously reported as morphine degradants in the literature. However, definitive safety qualification data do not exist. Should the required study demonstrate unacceptable general toxicity, the specifications will be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

General toxicology studies are required for drug product impurities that exceed the safety qualification threshold. Given the acute hospital use of this drug product, a study of 3 months is deemed adequate to definitively demonstrate that adequate safety margins exist for these impurities in the drug product, which can be used clinically for an extended period of time.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study is a repeat-dose toxicology study. The Applicant will test a mixture of the three impurities, [redacted](b) (4).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

KIMBERLY A COMPTON
11/10/2011

JUDITH A RACOOSIN
11/10/2011

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 19, 2011

To: Bob Rappaport, M.D., Director
Division of Analgesia, Anesthesia and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Morphine Sulfate Injection, NDA 202-515
Indication: Relief of mild to moderately severe pain
Dosages: Morphine Sulfate Injection in multiple strengths: 2 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, (b) (4), and multiple syringes (b) (4)
Company: Hospira

Materials reviewed: NDA 201-515 is located in EDR (Receipt Date: Jan 27, 2011)
\\CDSESUB1\EVSPROD\NDA202515\202515.enx
Previous PIND 105,936

Addendum

This is an addendum to our review of October 11, 2011, regarding NDA 201-515.

The recommendation on reports to the Agency is intended to comply with the standard reporting requirements for an approved NDA (21 CFR 314.80 and 314.81), and does not relate to the criteria for PMR/PMC (Section 130 of FDAMA 1997).

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/s/

ALICJA LERNER
10/19/2011

MICHAEL KLEIN
10/19/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

Application: N 202515

Name of Drug: morphine sulfate injection, USP

Applicant: Hospira, Inc.

Labeling Reviewed

Submission Date: January 14, 2011

Receipt Date: January 14, 2011

Background and Summary Description

Provides for injectable morphine sulfate indicated for the management of pain not responsive to non-narcotic analgesics. This is a 505(b)(2) relying on [redacted] (b) (4) N 018565 (Duramorph, by Baxter);

Filed March 15, 2011 with a PDUFA due date of November 14, 2011.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

In addition, the following labeling issues were identified:

1. Section titles "Microbiology," "Boxed Warning," "Clinical Studies," and "References," are listed in the Table of Contents (TOC) but are not present in the package insert (PI). Remove them from the TOC and Full Prescribing Information (FPI).

2. "Package Label," and "Principal Display Panel" are listed in the Table of Contents but are not part of the PI. Remove them from the TOC.

Recommendations

All labeling issues identified on the following pages with an "X" and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by April 19, 2011. The resubmitted labeling will be used for further labeling discussions.

Kim Compton, Regulatory Project Manager, February 25, 2011
Sara Stradley, Chief, Project Management Staff, March 23, 2011

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☒ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**." –

  This is presented in the PI twice. The 2nd one (not properly formatted) should be removed.

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☒ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.—

  This information appears twice. The 1st one should be removed as it contains an email address, which is not permitted.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

  ☒ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," –must appear at the end of HL. The revision date is the month/year of application or supplement approval. --

Is currently in incorrect format with date of last label revision.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**

☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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

/s/

KIMBERLY A COMPTON
10/17/2011
From March 2011 (not previously checked into DAARTS due to oversight)

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 11, 2011

To: Bob Rappaport, M.D., Director
Division of Analgesia, Anesthesia and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Morphine Sulfate Injection, NDA 202-515
Indication: Relief of mild to moderately severe pain
Dosages: Morphine Sulfate Injection in multiple strengths: 2 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, [redacted (b4)] and multiple syringes [redacted (b4)]
Company: Hospira

Materials reviewed: NDA 201-515 is located in EDR (Receipt Date: Jan 27, 2011)
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Previous PIND 105,936

Table of Contents

I. Summary

A. Background

This memorandum responds to the DAAAP consult regarding abuse potential of Morphine Sulfate Injection by Hospira. The sponsor submitted NDA 202-515 for the currently marketed, but unapproved, morphine sulfate product. This NDA is submitted as a 505(b)(2) application in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act. The Reference Listed Drug is Duramorph, NDA 018-565, by Baxter Healthcare and Morphine Sulfate Injection (in auto-injection system), (b4) (b4) A biowaiver for morphine sulfate injection

(b4)

The drug product is supplied in multiple strengths as indicated above. The product has the same recommended indication, dosage, and route and duration of administration as the previously marketed, but unapproved drug product.

B. Conclusions:

1. Morphine sulfate is listed as a Schedule II narcotic in the Controlled Substances Act.

C. Recommendations:

1. As a Schedule II drug under the CSA, all Schedule II narcotic regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of morphine sulfate injections should be in place and strictly followed.
2. Although this drug is primarily intended for use in the hospital setting, because of the current public health problem of prescription drug abuse, we request the sponsor submit the following additional information to FDA as periodic reports every 6 months for the first 2 years of marketing and then annually for the next 5 years:
   - Compile and analyze all postmarketing cases that relate to abuse, misuse, diversion and overdose of the product.
   - All sales to patients that occur outside of the hospital setting.

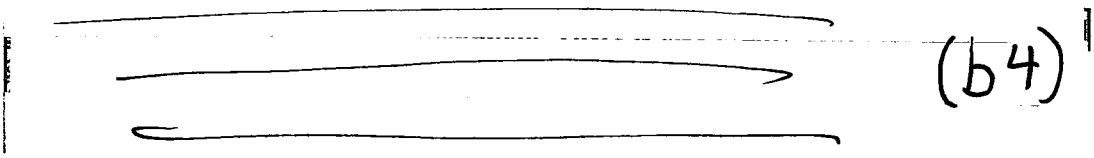
II. Discussion

A. Chemistry and Product Information

Morphine Sulfate USP (pentahydrate) is chemically designated as 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (1:1) (salt), pentahydrate, with molecular formula (C17H19NO3)2 • H2SO4 • 5H2O, and molecular weight 758.83. It is a white powder, which is soluble in water.

The sponsor proposes multiple strengths and packaging of the drug product: 2 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, and packaged in a Carpuject® or iSecure™ syringe,

(b4)



B. Pharmacology of drug substance and active metabolites

Morphine is a mu-opioid agonist, and exerts its therapeutic effect by mimicking the action of endogenous opioid peptides at opioid receptors. There are different types of opioid receptors: mu (μ) receptors are found primarily in the brainstem and medial thalamus. The adverse effects include respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation.

C. Clinical pharmacology

In humans, 34.0% to 37.5% of morphine is bound to plasma, largely to the albumin fraction and, to a lesser extent, to gamma globulin. Muscle tissue binding is reported at 54%. Morphine is metabolized in the liver by demethylation and glucuronidation, with the latter being the predominant mode of metabolism. In humans, the two main metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), following oral or parenteral administration. Approximately 10% of morphine is metabolized to M6G and 50% to M3G. 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% is excreted unchanged in the urine.

The half-life of morphine in young adults is about 2 hours. Maximum analgesia occurs approximately 20 minutes after intravenous administration and the analgesic effect persists for 2.5 to 7 hours. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours, and the elimination half-life is 1.5 to 2 hours.

D. Integrated assessment

During the reporting period of January 1, 1999 - December 12, 2008, there were 354 postmarketing reports that contained 624 adverse reactions: 98 were considered serious and 256 were non-serious.

During reporting period December 12, 2008 - December 2, 2010, there were 71 reports containing 163 adverse events, including 37 serious reports.

We identified: 32 deaths (Mod. 2.7.4 Clinical Safety, Table 10, page 59), 44 reports of overdoses (Table 16, page 68), and three reports of drug abuse (Table 11, page 66). At least 27 in 44 cases of reported overdose involved a pump (iv or intrathecal). Additionally, overdose in females comprised approximately 2/3 of all patients.

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/s/

ALICJA LERNER
10/11/2011

MICHAEL KLEIN
10/11/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	October 7, 2011
Reviewer(s):	Richard A Abate, RPh, MS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, MS, PharmD Division of Medication Error Prevention and Analysis
Division Director	Kellie Taylor, PharmD, MPH, Deputy Director Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Morphine Sulfate Injection, USP, 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, and 15 mg/mL syringes (Carpuject™ and iSecure™) (b) (4) [redacted]
Application Type/Number:	NDA 202515
Applicant/sponsor:	Hospira
OSE RCM #:	2011-214 2008-423

1 INTRODUCTION

This review evaluates of the proposed container labels and carton and insert labeling for Morphine Sulfate Injection, USP (NDA 202515) for areas of vulnerabilities that could lead to medication errors.

1.1 REGULATORY HISTORY

Although Morphine Sulfate Injection has been marketed in the United States for many years, the Agency began an initiative June 2006 to remove unapproved drugs from the market. In addition, the CDER's Office of Compliance took action against several companies producing morphine, hydromorphone, and oxycodone containing unapproved oral products March 2009. Thus, some manufacturers are submitting applications for the approval of currently marketed injectable unapproved opioid narcotic products.

NDA 202515, Morphine Sulfate Injection, USP, is a 505(b)(2) application with the reference listed drug, Duramorph, NDA 018565. The Applicant, Hospira, plans to market this product under the established name, Morphine Sulfate Injection, USP.

1.2 PRODUCT INFORMATION

Morphine Sulfate Injection, USP is an opioid agonist indicated to the management of pain not responsive to non-narcotic analgesics. The dose of morphine varies and is based on multiple patient factors including patient's pain and history of opioid medication use. Hospira proposes to package the product as prefilled syringes in both Carpuject™ and iSecure™ configurations in the following strengths: 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL, and 15 mg/mL. These presentations are for the administration of intermittent intravenous doses of morphine sulfate. (b) (4) prefilled syringe configurations are packaged in cartons containing ten syringes, and the vials are packaged individually. All presentations are stored at room temperature.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted July 22, 2011
- Carton Labeling submitted July 22, 2011

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted July 22, 2011
- Syringe (b) (4) samples provided August 5, 2011

Additionally, since Morphine Sulfate Injection, USP is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Hospira's Morphine Sulfate Injection products. The AERS search conducted on July 15, 2011 used the following search terms: active ingredient "Morphine," and "Morphine Sulfate." The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". As there are multiple manufacturers of Morphine Sulfate Injection, the manufacturer was limited to "Hospira%" (b) (4) No time limit was set. The ISR numbers of the retrieved reports are listed in Appendix C.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review.

(b) (4)

3 RESULTS AND DISCUSSION

The following section discusses the results of our AERS search and our evaluation of the labels and labeling.

3.1 MEDICATION ERROR CASES

A total of 96 reports were retrieved from our AERS search (See Appendix C for ISR numbers.) Following the exclusions described in Section 2, we evaluated a total of 38 cases relevant to this review. These cases are categorized below.

- Wrong Drug (n=27): These cases involve the administration of Morphine when it was believed to be another medication or another medication was administered when it was believed to be Morphine (n=8) or describe similarities between the products that could lead to wrong drug medication errors (n=19). The cases are described in Table 1 on page 3.

Table 1. Wrong drug medication errors

Wrong drug medication errors cases	**Number of Cases (N=8)** **Year received: (ISR numbers)**	**Medication ordered**	**Medication received**	**Causes or contributing factors identified from the report narratives**
	n=3 2001:(3667801) 2001:(3720119) 2003:(4258109)	Morphine	Hydromorphone *(All three cases did not specify in which direction the error occurred. Each case noted multiple errors, thus the error is likely occurring in both directions.)*	Similarity of the packaging, specifically the green needle/syringe tip shield which is seen in open carton in a narcotic cabinet. Additionally, DMEPA notes these two medications are frequently confused due to the similarity of the names and overlapping doses whether or not packaged in the Carpuject configuration.
	n=2 2003:(4127677) 2003:(4140072)	Morphine 10 mg/mL	Diazepam 10 mg/2 mL	EMS staff note the similarity of the packing of these two products from Abbott which resulted in the administration of the wrong medication.
	n=2 2005:(4821410) 2007:(5297382)	Morphine	Meperidine	The reporters note the syringe caps of the Carpujects are all green. Nurses open the cartons of Carpujects and only see the green syringe tops in the narcotics cabinet. During narcotic inventory counts or drug administration, the staff does not look into an open carton to check the drug has been returned or dispensed correctly.

	n=1 2006:(5097012)	Normal saline (NaCl 0.9%) flush	Morphine 10 mg/mL	Similar appearance of the Carpujects. The urgency of EMS attempting to resuscitate an 11 month old boy. Error occurred even though the medications are stored in two separate drug boxes.
Reports that describe similarities in products that have the potential for confusion that could result in wrong drug medication errors	**Number of cases and year reports received** **(N=19)**	**Medications with the potential to be confuse with Morphine injection due to packaging similarity.**		**Causes or contributing factors identified from the report narratives**
	n=7 (reported 2004 to 2007)	Heparin (The reports also noted similarity to Toradol and Ativan in the Carpuject packaging)		Similar appearance of the packaging including the green syringe tip shield/cover on all Carpujects
	n=6 (reported 2003 to 2007)	Hydromorphone (The reports also noted similarity to other strengths of Morphine, Meperidine, Promethazine, Dolasetron, Metoclopramide, and Diphenhydramine in the Carpuject packaging.)		Similar appearance of the packaging (ten syringes per carton, syringe in plastic tube, and five syringes banded together). Noted in all cases, the same green syringe tip shield/cover on all Carpujects. When the top of the carton is removed in a narcotic cabinet, the syringe tip is readily visible which adds to the similar appearance of these products.

	n=3 (1998 to 2004)	Meperidine (The reports also noted similarity to Anzemet in the Carpuject packaging)	Similar appearance of the packaging with a green syringe tip shield/cover on all Carpujects. Two 1998 cases (n=2) also note the similarity of the carton labeling included the same graphic stripe on the principle display panel which has been deleted by the Applicant.
	n=3 (reported 2003 tom 2006	Single report of these drugs: Trimethabenzamide, Ketoralac, and Midazolam	Similar appearance of the packaging including the green syringe tip shield/cover on all Carpujects

- Wrong Strength (N=7): These cases involve the selection of the wrong strength of Morphine sulfate packaged in the Carpuject syringe. The cases were reported from 1999 to 2009. All the cases identified the similarity of the Carpuject packaging design (green syringe tips) as a contributing factor. However, the two most recent cases also identified the fact that drug shortages had required the hospital to change the strength of Morphine Sulfate on the nursing units which contributed to these errors.
- (b) (4)
- (b) (4)

3.2 DEFICIENCIES ASSOCIATED WITH THE PACKAGING, LABELS AND LABELING

DMEPA discusses the deficiencies identified with the product packaging, Container labels and Carton labeling in the sections below.

3.2.1 Carpuject™ Syringes

The Carpuject™ packaging's visual appearance has contributed to medication errors. These syringes includes green syringe tip covers, a 2 mL graduated glass barrel, and similar printing on the label which is the common presentation on all Hospira products marketed in this packaging configuration. These similarities have resulted in wrong drug and wrong strength medication errors involving morphine sulfate.

(b) (4)

3.3 CONTAINER LABELS AND CARTON LABELING

(b) (4)

Some of the container labels are missing the statement "Not for epidural or intrathecal use" as required by the Morphine Sulfate Injection, USP monograph. The statement (b) (4) appears on the principle display panel of all container labels which incorrectly suggests to healthcare providers these products are safe to administer via epidural or intrathecal routes.

In addition, the abbreviation "IV" appears on some of the container labels to represent the route of administration. The abbreviation "IV" is often the misinterpretation of "error prone" abbreviations noted by the Institute of safe Medication Practices and not permitted in patient records by the Joint Commission.[2] Thus, DMEPA discourages the use of abbreviations on the container label and carton labeling.

The ONDQA reviewer requested DMEPA include the current acceptance criteria for pH to our comments (2.5 - 4.0).

3.4 INSERT LABELING

DMEPA provided comments to the insert label as part of the Division of Anesthesia and Analgesia Products. (b) (4)

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations http://www.ismp.org/Tools/errorproneabbreviations.pdf ; cited September 20, 2011.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the Carpujects™ (b) (4) packaging configurations have contributed to medication errors. In addition, the proposed container labels and carton labeling introduce vulnerability that can lead to medication errors because the information presented is inconsistent with the USP Monograph labeling requirements for Morphine Sulfate Injection. Finally, we note that the labels and labeling are cluttered making them difficult to find information and also missing some needed information required by the USP monograph. We recommend the following:

A. General Comments

1. We note that the needle assembly for the Carpuject syringes for all the strengths of Morphine Sulfate Injection are the same green color. This similarity has contributed to confusion between the strengths of morphine products and between products packaged in the Carpuject™ syringes. Thus, we recommend you consider using a variety of colors for the needle assemblies to help differentiate your products as well as the strengths of the same product, particularly those products and strengths that have been confused.
2. Delete the statement (b) (4) from of the principle display panel for all container labels and carton labeling.
3. Ensure that all carton labeling and the container labels for the (b) (4) presentations include the statement "not for epidural or intrathecal use" as required by the USP monograph. In addition, ensure this required statement is less prominent than the route of administration statement, 'For intravenous use."
4. Delete "[See USP Controlled Room Temperature]" from the side panels of all labels as it is redundant.
5. The current acceptance criteria for pH is 2.5 - 4.0. Revise Container labels and Carton labeling accordingly.

B. Container Labels

1. Carpuject syringes

a. All Strengths

Revise and reduce the font size of the scheduled drug designation (CII) as it detracts from the prominence of the established name and strength presentation.

b. 2 mg/mL strength

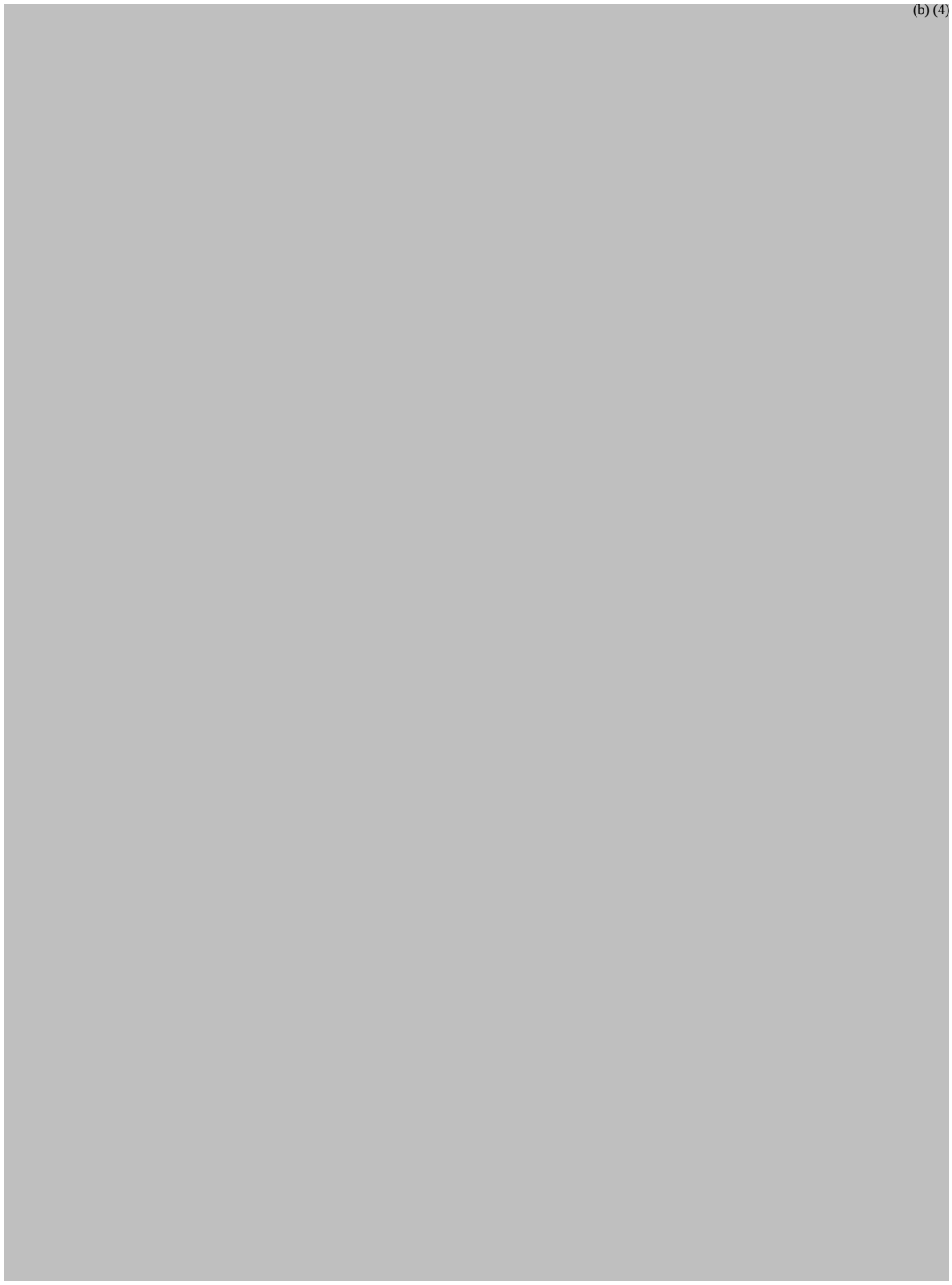
We note that the strength presentation appears in a different color font than the product name (purple vs. black). This presentation is inconsistent with the other strengths of prefilled syringes which present the established name and strength in the same color fonts. We recommend you revise the label to present the name and strength in the same color font. Select a color font (other than

purple) that is not the same or likely to be confused with another product packaged in Carpuject™ syringe.

2. iSecure™ syringes (2 mg/mL)

   See Comment B1b. Revise to be consistent with this strength presentation in the Carpuject configuration.

(b) (4)



C. Carton Labeling

1. Carpuject™ syringes

   a. All strengths

      The carton contain a net quantity of 10 syringes but the statement "1 mL" appears where the net quantity statement usually appears. Revise the net quantity statement to read "10 Carpujects, 1 mL each."

   b. 2 mg/mL syringe

      See Comment B1b.

2. iSecure™ syringes

   a. All strengths

      Revise the net quantity statement to read "10 x 1 mL syringe" or "10 x 1 mL cartridge." to describe the packaging configuration of the product.

   b. 2 mg/mL syringe

      See Comment B1b.

If the Division has further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

REFERENCES

Adverse Event Reporting System (AERS) database

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

Appendix A: Container Labels

(b) (4)

[redacted]

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Appendix C : ISR numbers of reports retrieved from the AERS

129337	3198869	3626366	4068279	4155971	4315394	4620571	5302155
4632201	3276312	3656414	4101167	4155820	4316788	4821410	5345525
4626855	3276280	3667801	4116813	4168467	4327811	4923422	5426082
4532632	3290711	3720119	4116414	4188170	4352132	4932952	5429307
971322	3290776	3762862	4116228	4195728	4381097	4979248	5519050
4609471	3349424	3786949	4123751	4209994	4381019	5004664	5523406
1458753	3359268	3796919	4127677	4209088	4402855	5097012	5545566
4532843	3515224	3815593	4138306	4243159	4458079	5152935	5871243
1743040	3515219	3874970	4140072	4248953	4510342	5175420	5916098
1999300	3532398	3879384	4155813	4258109	4595432	5232715	5986051
3007185	3563837	3895530	4155801	4258111	4620282	5290531	6123644
3021129	3601840	4009075	4155825	4265498	4620277	5297382	6784646

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/s/

RICHARD A ABATE
10/07/2011

LUBNA A MERCHANT
10/08/2011

KELLIE A TAYLOR
10/10/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: September 15, 2011

To: Kim Compton – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard – Professional Group Leader
Shenee Toombs – DTC Reviewer
DDMAC

Subject: **DDMAC draft labeling comments**
NDA 202515 morphine sulfate injection C-II

DDMAC has reviewed the proposed product labeling (PI), for Morphine Sulfate Injection C-II, submitted for DDMAC review on January 27, 2011. The following comments are provided using the substantially complete version of the labeling sent via email on September 08, 2011, by Kim Compton.

DDMAC's comments are provided directly in the attached marked-up copy of the PI. If you have any questions about DDMAC's comments, please do not hesitate to contact Mathilda Fienkeng at 301-796-3692 or at Mathilda.fienkeng@fda.hhs.gov.

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/s/

MATHILDA K FIENKENG
09/15/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 15, 2011
To:	Timothy T Jiang M.D. Medical Officer, Division of Anesthesia, Analgesia and Addiction Products (DAAAP) Office of New Drugs
Through:	Judy Staffa, PhD, RPh. Acting Director, Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology and Hina Mehta, Pharm.D. Drug Utilization Data Analysis Team Leader Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
From:	Rajdeep Gill, Pharm.D Drug Use Data Analyst Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
Subject:	Morphine Sulfate Injection Use in inpatient settings
Drug Name(s):	Morphine Sulfate
Application Type/Number:	202-515
Applicant/sponsor:	Hospira Inc.
OSE RCM #:	2011-1699

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Epidemiology (DEPI II) to provide inpatient utilization data on various strengths of morphine sulfate injection from year 2007 through 2010. Due to a substantial reporting of "unspecified strength" of morphine sulfate injection reported in inpatient hospital data, we also analyzed the sales data to obtain the most complete picture of national use of morphine sulfate injection from year 2007 through year 2010.

Sales data summary of findings:

- Approximately (b) (4) vials/boxes of syringes of morphine sulfate injection were sold in year 2010 a slight decrease from (b) (4) vials/boxes of syringes sold during year 2007
- Morphine sulfate 2mg/ml was consistently the most commonly sold strength throughout the time period examined
- Other commonly sold strengths of morphine sulfate injection were 4mg/ml, 10mg/ml, 5mg/ml and 1mg/ml.

Inpatient data summary of findings:

- Approximately (b) (4) discharges and (b) (4) unique patients were associated with a hospital billing for morphine sulfate injection in year 2010.
- For close to half of the billings for morphine sulfate in the hospital data, there was inadequate information to assess the concentration of the morphine product used; therefore we recommend extreme caution in interpreting the inpatient data
- Approximately (b) (4) discharges (19%) and approximately (b) (4) unique patients (19%) were associated with a hospital billing for morphine sulfate 2mg/ml in year 2010
- Other common strengths of morphine sulfate injection associated with a hospital billing include 4mg/ml, 10mg/ml, and 1mg/ml

1 BACKGROUND

1.1 INTRODUCTION

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) is reviewing a New Drug Application (NDA 202-515) for Morphine Sulfate Injection which is currently being marketed as an unapproved product. In support of that review, the Division of Epidemiology II (DEPI II) was consulted to provide data on the various strengths of morphine sulfate injection currently being used in the inpatient hospital setting. Using the currently available proprietary drug use databases licensed by the Agency, this review provides sales data and the number of unique patients and discharges associated with morphine sulfate injection, stratified by strength for year 2007 through 2010.

1.2 REGULATORY HISTORY

In 2006 a "Guidance for FDA Staff and Industry, Marketed Unapproved Drugs – Compliance Policy Guide" was put out describing how FDA intended to exercise an enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing[1]. Morphine sulfate injection manufactured by Hospira Inc. is currently being marketed without approval. The

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf

manufacturer has submitted an NDA for morphine sulfate injection to bring the agent in the approval process.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ data was used to determine the various channels of distribution for morphine sulfate injection. Sales data for year 2010 indicated that approximately 99% of morphine sulfate injection vials or boxes of syringes (Eaches) were distributed to non-retail settings (90% to non-federal hospitals)[2]. Therefore, we analyzed both sales distribution data as well as inpatient hospital data for various strengths of morphine sulfate injection.

2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. ***(See Appendix 1 for full database description)***

Inpatient hospital utilization was obtained from the SDI's Inpatient HealthCare Utilization System (IHCarUS) database to determine the number of projected unique patients and discharges associated with a hospital billing for morphine sulfate injection during years 2007 through 2010.

In addition, we also obtained sales data for various strengths of morphine sulfate injection from the IMS Health, IMS National Sales Perspectives™ from year 2007 through 2010 in number of "Eaches". The measure "Eaches" represents the number of single items (such as vials, syringes, bottles, or packet of pills) contained in a unit or shipping package and purchased by providers and pharmacies in a specific time period. An each is not a single pill or dosage of medicine (unless one package consists of a single dose). An each may be the same as a unit if the unit does not subdivide into packages.

3 DATA

3.1 SALES DISTRIBUTION DATA

Table 1 below shows the sales data for number of vials or boxes of syringes (Eaches) of morphine sulfate injection sold from the manufacturer to retail and non-retail settings of distribution stratified by strength from year 2007 through 2010. There has been a gradual decrease (-10%) in the amount of morphine sulfate injection sold from approximately (b) (4) vials/boxes of syringes sold in year 2007 to approximately (b) (4) vials/boxes of syringes sold in year 2010.

The most common strength of morphine sulfate sold was the 2mg/ml with approximately (b) (4) vials/boxes of syringes sold (38% of total morphine sulfate injection sales) during year 2010. Morphine sulfate 4mg/ml was associated with approximately (b) (4) vials/boxes of syringes sold (25% of total morphine sulfate injection sales) while morphine sulfate 10mg/ml was associated with approximately (b) (4) vials/boxes of syringes sold (18% of total morphine sulfate injection sales) in year 2010. The sales trends for the various strengths of morphine sulfate injection were relatively consistent throughout the four year study period.

[2] IMS Health, IMS National Sales Perspectives™. Year 2010, Extracted May 2011. File: 1105MSin.dvr

Table 1.

Number of Vials/boxes of syringes (eaches) of Morphine Sulfate injection sold (stratified by strength), Year 2007-2010								
	2007		2008		2009		2010	
	Eaches (in 000s)	Share %	Eaches (in 000s)	Share %	Eaches (in 000s)	Share %	Eaches (in 000s)	Share %
MORPHINE Injectable	(b) (4)							
2MG/ML								
4MG/ML								
10MG/M								
5MG/ML								
1MG/ML								
8MG/ML								
0.5MG/								
15MG/M								
10MG/1								
50MG/M								
25MG/M								
5MG/10								
500MG/								
200MG/								
50MG/5								
25MG/2								
15MG/1								
500MG								
20MG/2								
Source: IMS Health, IMS National Sales Perspectives™, years 2007-2010, extracted 06/11, File: 1106msin.xls								

3.2 *INPATIENT HOSPITAL DATA ON PROJECTED DISCHARGES AND UNIQUE PATIENTS*

Table 2 shows the number of projected discharges and unique patients associated with a hospital billing for morphine sulfate stratified by strength from year 2007 through 2010. There were a total of approximately (b) (4) discharges and (b) (4) unique patients associated with hospital billing of morphine sulfate injection in year 2010. The number of discharges and unique patients associated with a hospital billing for morphine sulfate injection appears to have increased slightly from approximately (b) (4) discharges and (b) (4) unique patients in year 2007.

The most common strength associated with a hospital billing of morphine sulfate injection was 2mg/ml with approximately 19% of the total discharges (about (b) (4) discharges) and 19% of the total unique patients (about (b) (4) patients) followed by the 4mg/ml strength with approximately 14% of total discharges (about (b) (4) discharges) and 14% of total unique patients (about (b) (4) unique patients) in year 2010. Other strengths commonly associated with a hospital billing for morphine sulfate injection were 10mg/ml and 1mg/ml during the time period studied.

Unfortunately, almost half of discharges and unique patients associated with a hospital billing for morphine sulfate injection were reported as "unspecified strength" with known weight (mg) of morphine sulfate, but the volume (ml) is unknown, making it difficult to ascertain the *true concentration* of morphine sulfate injection.

(b) (4)

Table 2.

Projected Number of Discharges and Unique Patients Associated with a Hospital Billing for Morphine Injectable by concentration, Year 2007-2010, Annually																
	Year 2007				Year 2008				Year 2009				Year 2010			
	Projected Discharges	*Share %*	Projected Unique Patients	*Share %*	Projected Discharges	*Share %*	Projected Unique Patients	*Share%*	Projected Discharges	*Share%*	Projected Unique Patients	*Share %*	Projected Discharges	*Share %*	Projected Unique Patients	*Share %*
Total																(b) (4)
2mg/ml																
4mg/ml																
10mg/ml																
1mg/ml																
0.5mg/ml																
30mg/30ml (1mg/1ml)																
8mg/ml																
15mg/ml																
150mg/30ml (5mg/1ml)																
25mg/ml (vial for dilution)																
50mg/ml																
200mg/20ml (10mg/ml)																
500mg/20ml (25mg/ml)																
Other known concentrations																
Total of other known mgs only																
Total of other known ml only																
Unspecified																
Source: SDI, Inpatient Health Care Utilization System (IHCarUS). Extracted July 2011, Source File: IHCarUS 2011-1699 Morphine Sulfate injection 07-08-11.xls																

The total of all the strengths may add up to more than 100% because one unique patient could be getting multiple strengths of morphine sulfate injection during one hospital visit.

****Do not add across columns or rows. Summing across columns or rows will result in double-counting and overestimates of patient count.***

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that morphine sulfate injection (various strengths) was distributed primarily to non-retail settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible *surrogate for use*, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The SDI Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals, and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the SDI CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of SDI's Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown SDI's patient level data to be representative and accurate across multiple therapeutic areas.

The utilization data of various strengths of morphine sulfate was difficult to assess due to unspecified product reporting in the inpatient hospital data, therefore, we analyzed sales data as a *surrogate of use* to obtain the most complete picture of national use for various strengths of morphine sulfate. A vast majority of the unspecified concentrations was associated with known weight of morphine sulfate (in mgs) but unknown volume (mls), making it difficult to ascertain the true concentration of morphine sulfate injection. So, the inpatient data trends should be interpreted with caution because of high reporting of "unspecified" strengths of morphine sulfate injection.

We do not recommend adding across columns or rows in the table providing inpatient data. Summing across columns or rows will result in double-counting and overestimates of patient count.

(b) (4)

5 CONCLUSIONS

National inpatient utilization of various strengths of morphine sulfate injection was difficult to ascertain due to limited information or "unspecified" strengths of morphine sulfate injection in the billing data. Therefore, sales data was analyzed to provide a complete picture of national use of morphine sulfate injection. Overall, sales of morphine sulfate injection appears to be decreasing over the examined time period, with morphine sulfate 2mg/ml strength being associated with the majority of sales followed by 4mg/ml and 10mg/ml. In contrast to the national sales data, the inpatient hospital data suggest that the number of discharges and unique patients associated with a hospital billing of the various strengths of morphine sulfate are increasing slightly; but similar to sales data; morphine sulfate 2mg/ml, 4mg/ml and 10mg/ml were the most commonly used strengths in the inpatient settings from year 2007 through year 2010.

APPENDIX 1. DATABASE DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Inpatient HealthCare Utilization System (IHCarUS)

SDI's Inpatient HealthCare Utilization System provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days after the end of each monthly period. This robust data set includes > 650 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >7 million annual hospital inpatient encounters and >60 million annual hospital outpatient encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. SDI's datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The SDI Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals, and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the SDI CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of SDI's Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown SDI's patient level data to be representative and accurate across multiple therapeutic areas.

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

/s/

RAJDEEP K GILL
07/15/2011

HINA S MEHTA
07/15/2011

JUDY A STAFFA
07/15/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information	
NDA # 202515	
Proprietary Name: None Established/Proper Name: Morphine sulfate injection, USP Dosage Form: Injection (IV (b) (4)) Strengths: 2, 4, 8, 10, 15, (b) (4) mg/mL	
Applicant: Hospira, Inc. Agent for Applicant (if applicable):	
Date of Application: 1-14-2011 Date of Receipt: 1-14-2011	
PDUFA Goal Date: 11-14-11	Action Goal Date (if different): 11-10-11
Filing Date: 3-15-11	Date of Filing Meeting: 2-28-11
Chemical Classification: (1, 2, 3 etc.) (original NDAs only) 7	
Proposed indication(s)/Proposed change(s): Management of pain not responsive to non-narcotic analgesics	
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: Unapproved, marketed drug	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): PIND 105936	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			No proprietary name, firm states not proposing one
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	Y			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
N 022321	Embeda (morphine sulfate/naltrexone HCl)	NC	8-13-2012

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:***		X		

http://www.fda.gov/cder/ob/default.htm				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**x**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**x**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			(Attmt; in separate folder)
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		The firm is not claiming any patents on any part of their product.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*		X		There is no signed form, just a note that there were no clinical studies conducted so nothing to disclose.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			(submitted as amendment 2)
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with	X			

authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* 1-27-11 <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	**X**			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		Sponsor has stated they will not be proposing one
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting***		X		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10-28-09 ***If yes, distribute minutes before filing meeting***	X			This was called a PIND mtg in the system, but it was really Pre-NDA, a copy has been saved to the NDA share drive and a link sent to the team.
Any Special Protocol Assessments (SPAs)?		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-28-11

NDA: 202515

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: morphine sulfate injection, USP

DOSAGE FORM/STRENGTH: IV(b) (4) injection

APPLICANT: Hospira, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Management of pain not responsive to non-narcotic analgesics

BACKGROUND: This is a marketed, unapproved product. The company had a Pre-Submission Meeting with the Agency 10-28-09 (PIND 105936.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton	Y
	CPMS/TL:	Sara Stradley	Y
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Tim Jiang	Y
	TL:	Ellen Fields	Y
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	N/A	
	TL:	Dionne Price (PRN only)	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y

Product Quality (CMC)	Reviewer:	Ying Wang	Y
	TL:	Prasad Peri	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Bryan Riley	N
	TL:		
CMC Labeling Review	Reviewer:	Per Swati, will lblg rvw will be conducted by assigned CMC rvwr	
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	Y
	TL:	Mike Klein	N
Other reviewers	Twyla Thompson (N) and Mathilda Fienkeng (N), DDMAC Rvwrs; Minerva Hughers (Y), Biopharmaceutics Rvwr; Richard Abate (Y), DMEPA lblg rvw; Melina Griffis (N), DMEPA TL		(see Y or N following individual names at left)
Other attendees	Danyal Chaudhry (Y), OSE PM; Swati Patwardhan (Y), ONDQA PM; Tia Harper-Velazquez (Y), DNDLC, OC; Lori Canton (Y), DNDLC, OC; Lauren Choi (Y), TL, DPVI, OSE		(see Y or N following individual names at left)

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: [Application contains no clinical studies.]	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES

Comments: Ranaan Bloom is assigned to review	☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Bryan Riley is assigned reviewer	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES on 2-9-11 ☐ NO
CMC Labeling Review **Comments**: Per Swati, lblg rvw will be conducted by assigned CMC rvwr	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Bob Rappaport

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): milestones are listed on the Filing/Planning mtg Agenda in brief and the GRMP timeline is completed and saved in the share folder for this NDA

Comments:

Primary Rvws due by 10-10-11
Secondary Rvws due by 10-17-11
Send proposed Lblg and PMC/R to firm by 10-17-11
Action goal date: 11-10-11

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues:

	☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

KIMBERLY A COMPTON
03/31/2011

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 18, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA** 202-515
Indication: Relief of mild to moderately severe pain
Dosages: Morphine Sulfate Injections in multiple strengths: 2 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, (b) (4) and multiple syringes (b) (4)
Company: Hospira

Materials reviewed: NDA 201-515 is located in EDR (Receipt Date: Jan 27, 2011)
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Previous PIND 105,936

Table of Contents

A. Background:

This memorandum responds to the DAAP consult regarding abuse potential of Morphine Sulfate Injection by Hospira. The sponsor submitted NDA 202-515 for the currently marketed, but unapproved, morphine sulfate product. This NDA is submitted as a 505(b)(2) application in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. The Reference Listed Drug is Duramorph®, NDA 018-565, by Baxter Healthcare and Morphine Sulfate Injection (in auto-injection system), NDA 019-999, (b) (4)

(b) (4) The sponsor submitted a request for waiver of pediatric studies and a bioequivalence waiver request.

The present submission includes a CMC section and based on literature review non-clinical overview and summaries of clinical pharmacology, bioavailability and safety. The summary of clinical safety also includes pharmacovigilance data collected by Hospira in the post-marketing setting.

The drug product is supplied in multiple strengths: 2 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml, and packaged in a Carpuject® or iSecure™ syringe, (b) (4)

This product has the same recommended indication, dosage, and route and duration of administration as the previously marketed, but unapproved drug product.

The sponsor has no questions specific for CSS, but DAAP requests input from CSS regarding this NDA.

B. Conclusion

In this NDA, the sponsor provided non-clinical and clinical information based on the reviewed literature and additional safety data based on Post-Marketing Data collected by Hospira.

C. Recommendation (to be relayed to the Sponsor)

1. List all AEs reported during post-marketing period broken down by dose range 2-15 mg/ml (b) (4) and by gender. A separate table should be provided for elderly patients. Adverse events should be MedDRA coded or at least provided by organ systems. The sponsor's data should be separated from literature derived cases.

2. Provide a table for all AEs reported during 41 randomized controlled clinical trials mentioned in NDA (Mod 2.7 Clinical summary) broken down by dose range 2-15 mg/ml (b) (4) by gender and by mode of use (iv/ (b) (4) The present tables 8 and 9 (Mod 2.7 Clinical summary) are not adequate and not informative because they provide mainly general information about the study design and just few AEs are mentioned; we request a table which includes all AEs MedDRA coded summarized from all the 41 clinical trials. Additionally, include withdrawal cases due to AEs.

3. Provide short summaries of twenty 15-Day Reports for morphine sulfate that were submitted to the FDA (Dec 2008-Dec 2010) and any other reports from previous years, if they exist.

APPEARS THIS WAY ON ORIGINAL

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

/s/

ALICJA LERNER
03/18/2011

MICHAEL KLEIN
03/18/2011