CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202515 SUPPL # HFD # 170

Trade Name morphine sulfate injection

Generic Name

Applicant Name Hospira

Approval Date, If Known: 11/14/2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(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
Various ANDAs		Extended-release morphine sulfate tablets and morphine sulfate injectables

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and

effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kim Compton, Sr. Project Manager, 11/2/2011
Name of Division Director signing form: Sharon Hertz, M.D., Deputy Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

SHARON H HERTZ
11/14/2011

Hospira

Generic Drug Enforcement Act of 1992 Certification

Morphine Sulfate Injection USP

Section 306(k) of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992 (GDEA), requires that:

> "Any application for approval of a drug product shall include
>
> (1) a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) in connection with such application, and
>
> (2) if such application is an abbreviated new drug application, a list of all convictions, described in subsections (a) and (b) which occurred within the previous five (5) years, of the application and affiliated persons responsible for the development or submission of such application."

Hospira, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under section 306 of the Act in connection with this application.

Hospira, Inc. hereby states that it has no such convictions to list.

10-25-2010

Date

Melissa A. Nguyen
Product Manager, Regulatory Affairs
Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2
Lake Forest, IL 60045-5046

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 20215 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Anesthesia, Analgesia, and Addiction Products PDUFA Goal Date: 11/14/11 Stamp Date: 1/14/2011

Proprietary Name: none

Established/Generic Name: morphine sulfate injection, USP

Dosage Form: injection

Applicant/Sponsor: Hospira

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): ____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Management of pain not responsive to non-narcotic analgesics

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

✦ Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

ection C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

Kim Compton (not entered in DARRTS), 11/2/11

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202515 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: none Established/Proper Name: morphine sulfate injectionUSP, 2, 4, 8, 10, 15, (b) (4) mg/mL Dosage Form: injection		Applicant: Hospira, Inc. Agent for Applicant (if applicable):
RPM: Kim Compton		Division: Division of Anesthesia, Analgesia, and Addiction Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

N 018565, DuramorphPF (morphine sulfate injection, USP), 0.5 mg/mL and 1.0 mg/mL

Provide a brief explanation of how this product is different from the listed drug.
This NDA product will be approved only for IV administration. (b) (4)

The listed product is approved for IV, (b) (4)

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 11/14/11

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

• Proposed action • User Fee Goal Date is 11/14/2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 7

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic. **The firm specified that they were not claiming any patents on any part of their product, so no form is submitted.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  ☐ Yes ☐ No

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

  ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  ☐ Yes ☐ No

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

  ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	11/14/11
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP, 11/14/11
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	See label attached to AP letter
• Original applicant-proposed labeling	1/14/2011
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	11/11/2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 10/17/2011 ☒ DMEPA 10/10/2011and 11/14/2011 ☐ DRISK ☒ DDMAC 9/15/2011 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Rvw, 3/31/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 11/3/2011
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 11/8/2011
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: the products that are the subject of this application do not represent a change in active ingredient, dosage form, route of administration, indication or dosing regimen, therefore, the pediatric study requirements under PREA are not applicable • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included (various dates)
❖ Internal memoranda, telecons, etc.	11/14/2011
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12/8/2009
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/14/2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None 5
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	None
• Clinical review(s) *(indicate date for each review)*	10/6/2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	See Summary Decision Memo, page 8
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not applicable 3/18/2011; 10/11/12011; 10/19/2011
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3/10/2011; 10/20/2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/9/2011; 6/16/2011; 10/14/2011; 10/26/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 4/5/2011; 10/5/2011; and 11/10/2011 (CMC) 3/2/2011; 6/30/2011 (Biopharmaceutics)
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 9/29/2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	5/12/2011
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE’s ADRA.

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/s/

KIMBERLY A COMPTON
11/14/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, November 10, 2011 10:35 AM
To: 'Nguyen, Melissa'
Subject: Morphine carton and container labeling for carpujects

Hi Melissa,

In reviewing the carton and container labels for the carpujects, our Division of Medication Error and Prevention had the following change requests.

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

The use of the same black field behind the strengths 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 behind the drug name to include the strength. We recommend you leave the 2 mg/mL strength as proposed.

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

See Comment A.

Do you think you can make these changes and submit revised versions (again, does not have to be FPL) by tomorrow? We need to attach the agreed-upon version to our letter.

Thanks

Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
11/14/2011

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 9, 2011
TIME:	2:15 PM Eastern
LOCATION:	Teleconference
APPLICATION:	NDA 202515
DRUG NAME:	morphine sulfate injection, USP
SPONSOR:	Hospira, Inc.
MEETING RECORDER:	Kim Compton, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FDA ATTENDEES:

Sharon Hertz, Deputy Director, DAAAP
Sara Stradley, Chief Project Management Staff, DAAAP
Kim Compton, Project Manager, DAAAP
Jouhayna Saliba, Drug Shortages Staff
Bryan Riley, Microbiologist
Danae Christodoulou, Chemistry Lead
Prasad Peri, Chemistry Branch Chief
Eric Duffy, Chemistry Division Director
Catherine Gould, Office of Compliance (OC)
Helen Saccone, OC, Office of Manufacturing and Product Quality (OMPQ)
Tamara Felton, OC, OMPQ
Teddi Lopez, OC, OMPQ
Sakineh Walther, OC, Office of Unapproved Drug Labeling Compliance (OUDLC)
Judith McMeekin, OC, OUDLC
Tia Harper-Velazquez, OC, OUDLC
Israel Santiago, OC
Derek Smith, OC, OMPQ

EXTERNAL CONSTITUENT (Hospira, Inc.) ATTENDEES:

Mike Ball, CEO
Eric Floyd, Vice-President, Global Regulatory Affairs
Lisa Zboril, Director, Global Regulatory Affairs
Melissa Nguyen, Product Manager, Global Regulatory Affairs
Sandeep Shiroor, Director, Pharma R&D
Francioux Gueffier, Group Leader, Pharma R&D
Edward Koo, Director, Preclinical Development
Lee Reif, Program Management
Francois Dubois, Vice-President, Quality
Brian Smith, Counsel

BACKGROUND: This NDA contains several presentations of morphine sulfate injection in both pre-filled syringes (b) (4) The products under this NDA are currently marketed as unapproved products. They are medically necessary and constitute a large percentage of the injectable morphine market. The injectable opioid market is already in shortage on fentanyl, another injectable opioid and the Agency wants

to avoid any additional shortages of injectable opioids to avert a public health crisis. There is a manufacturing site issue precluding approval of the application as it was originally submitted.

The Hospira manufacturing site at (b) (4) has on-going cGMP deficiencies that could not be resolved before the PDUFA goal date of Monday, November 14, 2011. This site is responsible for the manufacturing of drug product (b) (4). With the overall withhold recommendation for the site, the NDA cannot be approved. A path forward to allow marketing of this medically necessary product needs to be found, if possible.

The Carpuject and iSecure pre-filled syringe presentations are manufactured at the McPherson, KS site which has an "acceptable" recommendation from the Office of Compliance.

MEETING OBJECTIVES: To reach agreement on a path toward approval action for at least a portion of the products in the application and emphasize to the firm the need to continue marketing all presentations of the product to avoid a drug shortage.

DISCUSSION POINTS:

- **The Agency inquired if the Sponsor could move manufacturing of the (b) (4) of the product to the KS site that currently manufactures the pre-filled syringes. The sponsor is going to look into this possibility, but since they had no data on this, did not believe they could complete any change before the action date of November 14, 2011.**
- **The Agency inquired if the Sponsor would then be willing to withdraw (b) (4) site and (b) (4) produced there from the application to allow the (b) (4) manufactured at the McPherson, KS, site to be approved. The Sponsor agreed.**
- **The Agency emphasized the importance of all presentations of the product continuing to be available on the market and requested that the Sponsor continue marketing them all, even with approval of only the syringe presentations in order to avoid a drug shortage of this medically necessary product. The sponsor stated that they would continue marketing as they had been and committed to notify the Agency if they became aware of anything that might lead to a shortage of the products.**
- **The Agency requested that the sponsor revise their labeling to remove reference to the (b) (4) and submit that, along with their request to withdraw (b) (4) site from the application. The Sponsor agreed to this.**

DECISIONS (AGREEMENTS) REACHED:

The Sponsor planned to submit a request to remove the (b) (4) manufacturing site, and presentations made there, from the application. In addition, they planned to submit tracked, updated labeling removing reference to the (b) (4).

At the request of the Agency, the Firm will continue to market the (b) (4) as they have been in order to avoid a drug shortage situation of this medically necessary product. They will work to either relocate manufacturing of the (b) (4) to the approved KS site if possible, or, if not, will continue to work to resolve the deficiencies at their (b) (4) Site (b) (4)

ACTION ITEMS AND POST MEETING FOLLOW-UP:

1. The firm will submit an amendment to the application withdrawing [redacted] site and [redacted] manufactured there, as well as an amended label (PI) to remove reference to the [redacted]. **This was received by the Division on November 9, 2011.**

2. Once Action item #1 above is received by the Agency, the Chemistry team will cancel the EES request for the [redacted] site. **This was completed on November 9, 2011.**

3. Once Action item #2 is complete, the Office of Compliance will update the EES recommendation to "acceptable." **This was completed on November 10, 2011.**

4. Once Action item #3 is complete, the Chemistry team will enter an addendum in DARRTS stating that the presentation of the iSecure and Carpuject syringes may be approved. **This was completed on November 10, 2011.**

5. The team will review the amended PI to ensure it is acceptable. **This action was complete on November 10, 2011**

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/s/

KIMBERLY A COMPTON
11/14/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, October 28, 2011 5:48 PM
To: 'Nguyen, Melissa'
Cc: Compton, Kimberly
Subject: RE: FDA replies for Morphine Sulfate Injection, USP (NDA 202515) Carton and container label comments from firm
Attachments: N 202-515 copy of PI FROM SPONSOR 10-26-11-- USE FOR EDITS.doc

Hi Melissa,

The team reviewed the rest of the Carton and Container labels and has only this one remaining comment:

> FDA Response to A. General Comment #1:
> Given the fact that the FDA has not received reports of wrong drug medication errors related to the use of Morphine Carpujects recently, we have no objection to the use of the green syringe caps for the Carpujects. However, the Agency will continue watchful monitoring for medication error reports of this type involving the Carpujects. Should we receive reports of similar errors in the future, we will request changes be made to the Carpujects to address any confusion between products.

Therefore, please do go ahead to plan to submit final carton and container labels as you are now in receipt of all of our comments.

In addition, we looked over the returned PI and have only a few outstanding items. They are tracked and noted in the attached copy. Please review with your team and let us know if you can agree to these revisions. If so, please also submit finalized PI as soon as that is available. Please let me know if you need to discuss any of these revisions further however.

Thanks and have a nice weekend,
Kim

From: Nguyen, Melissa [mailto:melissa.nguyen@hospira.com]
Sent: Friday, October 28, 2011 1:49 PM
To: Compton, Kimberly
Subject: RE: FDA replies for Morphine Sulfate Injection, USP (NDA 202515) Carton and container label comments from firm

Hi Kim,

We have revised the Carton and Container labels for NDA 202515 morphine sulfate. Can you confirm if additional comments are still forthcoming (most likely Carpuject) and when we can expect to receive the comments, if any, from the FDA to incorporate in the final printed labeling?

I can provide a representative copy of the current Carton and Container labels for the Carpuject (2 mg/mL) for review if you think this would be helpful to the FDA reviewer. Please let me know.

Thanks,
Melissa

From: Nguyen, Melissa
Sent: Tuesday, October 25, 2011 3:15 PM
To: 'Compton, Kimberly'
Subject: RE: FDA replies for Morphine Sulfate Injection, USP (NDA 202515) Carton and container label comments from firm

Hi Kim,

Hospira has accepted the Agency's recommendation below and will revise the Carton and Container labels accordingly.

Thanks,
Melissa

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Monday, October 24, 2011 4:12 PM
To: Nguyen, Melissa
Subject: FDA replies for Morphine Sulfate Injection, USP (NDA 202515) Carton and container label comments from firm

Hello Melissa,

The team here has looked over the Carton and Container responses you sent last week on Oct 19, and have the following replies. We are still having internal discussion on a few of the others, so expect to follow this up with some additional comments later in the week, most likely on the carpuject issue (General Comment #1).

> FDA Response to A. General Comment #2:
> FDA agrees "Preservative Free" should be included on the label as noted in the USP monograph for Morphine Sulfate, Inj. However, we do not believe it should appear on the principle display panel of the labels for these products as the prominence of this information has contributed to medication errors.
>
> We identified medication errors in which practitioners see specific terms on labels (e.g., single-dose (b) (4) or preservative free) and mistakenly believe that these products are safe for the compounding of sterile products for epidural administration. These errors occurred even though the product labels also included the caution "Not for epidural or intrathecal use" which was overlooked. Although the products in this application do not contain any preservative, they include the antioxidant, sodium edetate, which cannot be administered by these routes.
>
> (b) (4)

(b) (4)

[redacted]

FDA Response to A. General Comment #4: We recognize the USP states that the storage conditions must be included on product labels. However, FDA has identified two citations (USP General Chapter 1150 Pharmaceutical Stability and General Notice 10 PRESERVATION, PACKAGING, STORAGE, AND LABELING, specifically 10.30.60 Controlled Room Temperature) which state the products may be labeled with a temperature range "up to 25 C" or at "Controlled Room temperature." The proposed Container labels and Carton labeling include both.

The side panels are cluttered with information. The temperature range is included and is more specific and useful to healthcare providers. Thus, we believe that the "[USP controlled Room Temperature]" statement should be removed to improve readability of other important information on the labels.

Please let me know if Hospira needs to discuss any of these points or if you feel you can accept the Agency recommendations on these.

Thanks
Kim

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

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/s/

KIMBERLY A COMPTON
10/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515 **DISCIPLINE REVIEW LETTER**

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your January 14, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

We also refer to your submission dated July 14, 2011.

Our review of the brief summary of the study design for the 13-week toxicity study in rats for the morphine impurities is complete, and we have the following comments:

1. The use of a mixture of the three impurities is acceptable.

2. The proposed dose levels (1 and 3 times the human equivalent dose) are acceptable provided adequate coverage is demonstrated at the maximum daily dose of 722 mg for morphine.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARA E STRADLEY
10/28/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Tuesday, October 18, 2011 6:36 PM
To: 'Nguyen, Melissa'
Cc: Compton, Kimberly
Subject: marked up copy of morphine sulfate PI

Attachments: N 202-515 WORKING copy of PI (from EDR 7-26-11)-- USE FOR EDITS.doc

Hi Melissa

The team has entered the changes they believe are needed in the morphine PI. They are marked in track changes mode in the attached WORD copy for you to easily see our recommendations, notes, etc.

Please see the attached file, share and review with your team. Accept all changes Hospira is OK with, and, in tracked changes mode, make notes or counter-recommendations that Hospira wants instead and return the marked up WORD file of the PI to us via email marked accordingly. We request that back to us by close of business next Tues, Oct 25, but please let me know if more time is needed.

N 202-515
ORKING copy of PI (

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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/s/

KIMBERLY A COMPTON
10/25/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, October 14, 2011 7:05 PM
To: 'Nguyen, Melissa'
Cc: Compton, Kimberly
Subject: Container and Carton labeling comments

Hi Melissa,

We have the following comments on the Carton and Container labeling for the morphine sulfate NDA (202515). We expect to have comments on the package insert (marked in the document as tracked changes) to share with you in the next few days as well.

I will archive copies of these communications so we have a record of what we've sent Hospira.

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 [redacted] (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 [redacted] (b) (4) include the statement [redacted] (b) (4) as required by the USP monograph. In addition, ensure this required statement is less prominent than the route of administration statement, [redacted] (b) (4) intravenous use."
4. Delete [redacted] (b) (4) 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

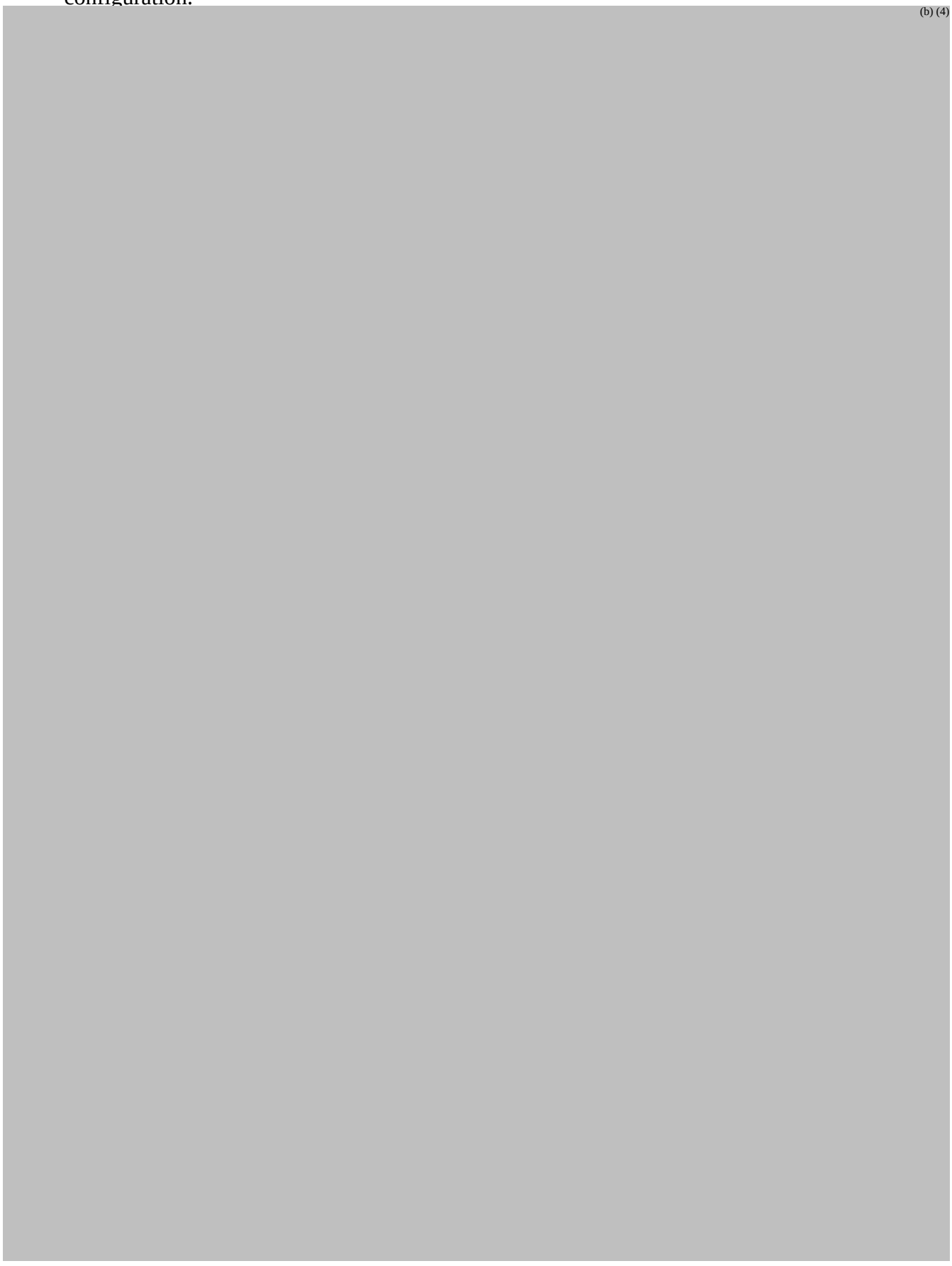
Revise and reduce the font size of the scheduled drug designation (CII) as it detracts from the prominence of the established name and strength presentation.

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.

Please let me know if you have any questions or concerns about our comments and when you think you can send us revised labeling.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products

301-796-1191

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/s/

KIMBERLY A COMPTON
10/17/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515

DISCIPLINE REVIEW LETTER

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your January 14, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

We also refer to your submission dated March 22, 2011.

Our review of the clinical section of your submission is complete, and we have identified the following deficiencies:

(b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARA E STRADLEY
10/13/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, September 09, 2011 7:17 PM
To: 'Nguyen, Melissa'
Cc: Compton, Kimberly
Subject: question on N 202-515

Hi Melissa,

Our microbiologist has the following request for the Morphine NDA:

(b) (4)

Please let me know if you have any questions about our request and when you think you might be able to provide a reply.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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KIMBERLY A COMPTON
09/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Kimberly Compton, Sr. Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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SARA E STRADLEY
09/07/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, August 11, 2011 10:13 AM
To: 'Nguyen, Melissa'
Subject: Re: Information request for NDA 202515

Dear Melissa,
We are reviewing CMC section of your application and have following information request

- **Your proposed acceptance criterion for pH of (b) (4) in the drug product is too wide and is not supported by the batch data and the pharmaceutical development report. pH is identified as a critical quality attribute and should be controlled accordingly. Tighten the acceptance criterion for pH (e.g., 2.5-4.0) in the drug product or provide justification to support your proposal.**

Please acknowledge the receipt and provide a tentative timeline for the response.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
08/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515

DISCIPLINE REVIEW LETTER

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your January 14, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

Our review of the biopharmaceutical section of your submission is complete, and we have the following comments regarding your request for a waiver of the requirement to provide in vivo bioavailability or bioequivalence data (i.e., a biowaiver):

1. A biowaiver is granted for morphine sulfate injection administered by the intravenous route only.

2. (b) (4)

3. Revise and resubmit your labeling to remove references to the (b) (4) administration for this product.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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SARA E STRADLEY
07/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515 **INFORMATION REQUEST**

Hospira, Inc.
Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Dear Ms. Nguyen:

Please refer to your January 14, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your proposed acceptance criterion for total impurity of NMT (b) (4) in the drug substance is not supported by the batch data. Discuss this with the DMF holder and tighten the acceptance criterion or provide justification for your proposal.

2. Provide detailed information for your extractable/leachable study; including solvent/formulation used, etc. Provide quantitative results for any extractable/leachable components detected.

3. Your proposed acceptance criterion of (b) (4) for edentate disodium in the drug product is not supported by the batch data. Tighten the acceptance criterion or provide justification for your proposal.

4. Your proposed acceptance criterion for total impurity of NMT (b) (4) in the drug product is not supported by the batch data. Tighten the acceptance criterion or provide justification for your proposal.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515

DISCIPLINE REVIEW LETTER

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your January 14, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

Our review of the nonclinical section of your submission is complete, and we have identified the following deficiencies:

1. Your drug substance acceptance specification of (b) (4) for (b) (4) exceeds the ICH Q3A(R2) qualification threshold. We recommend that you consult with your DMF holder and tighten your acceptance specification to NMT 0.15% in order to comply with ICH Q3A(R2) guidelines.

2. The drug product specifications for (b) (4) exceed the ICH Q3B(R2) qualification threshold of NMT 0.2%. Your literature-based justification is not adequate to support the safety of your proposed drug product specifications. However, the genetic toxicology studies with (b) (4) are acceptable and no further genetic toxicology qualification of (b) (4) will be required.

   The impurities/degradants must either be reduced to below ICH Q3B(R2) qualification threshold of NMT 0.2% or adequately qualified via toxicology studies. Adequate qualification would include:

   a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) for (b) (4), tested up to the limit dose for the assay.

b. Repeat dose toxicology studies of 90 days duration with (b) (4) .

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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SARA E STRADLEY
06/20/2011

Compton, Kimberly

From: Compton, Kimberly
Sent: Tuesday, May 10, 2011 1:01 PM
To: 'Nguyen, Melissa'
Cc: Compton, Kimberly
Subject: Information Request for N 202-515, morphine sulfate

Hi Melissa,

Please provide the expected clinical use of the following configurations of morphine sulfate in NDA 202-515; this may be based on past usage data:

- Prefilled syringes:
  - 2mg/ml: IV, (b) (4)
  - 4mg/ml: IV,
  - 8mg/ml: IV,
  - 10mg/ml: IV, (b) (4)
  - 15mg/ml: IV,
  - (b) (4)
  -

For the (b) (4).

Please let me know if you have any questions about our request.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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KIMBERLY A COMPTON
05/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515

FILING COMMUNICATION

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your New Drug Application (NDA) dated January 14, 2011, received January 14, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL.

We also refer to your submission(s) dated January 25, February 11, and March 7, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 14, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 17, 2011.

During our filing review of your application, we identified the following potential review issues:

1. We note that there are several specifications for drug product impurities that exceed thresholds set by the ICH Q3B guideline. Upon preliminary review, the literature

references that you submitted do not appear to support the safety of your proposed specifications. Specifically, the references do not quantify levels of the morphine metabolites [redacted]. The literature references provided to toxicologically qualify [redacted] do not contain an adequate histopathologic assessment. If upon formal review your justification for the safety of these impurities is not deemed adequate by current toxicology standards these impurities/degradants must either be reduced to below ICHQ3A/B qualification thresholds or adequately qualified via toxicology studies.

a. Adequate qualification generally would include:

i. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with [redacted], tested up to the limit dose for the assay.

ii. Repeat dose toxicology studies of 90 days duration with [redacted].

2. Provide an updated stability summary for the primary stability batches included in the NDA. In addition, provide updated stability data in inverted configurations, e.g., [redacted] Carpuject® and iSyringe® cartridges.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. List all Adverse Events (AE) reported during the post-marketing period broken down by dose range 2-15 mg/ml [redacted] and by mode of use (intravenous [redacted] injection [redacted]) and by gender.

a. Provide a separate table for events by age. Adverse events should be MedDRA coded or at least provided by organ systems.

b. Separate data on Hospira products covered under this application from literature-derived cases.

c. Provide a separate listing for AEs that would have been considered unexpected and unlabeled and that would have resulted in 15-Day reports sent to FDA had an NDA been in place, with summaries of these cases.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

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.

3. In Highlights (HL), there is redundancy of information.

    a. The 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 iteration, which does not follow the proper format, should be removed.

    b. 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 first one should be removed as it contains an email address, which is not permitted.

4. **The Revision Date** should have a placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," and must appear at the end of HL. The revision date is the month/year of application or supplement approval. It is currently in incorrect format showing the date of the last label revision.

We request that you resubmit labeling that addresses these issues by April 19, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ on behalf of BOB A RAPPAPORT
03/29/2011
Signing for Bob Rappaport, M.D.

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, March 07, 2011 8:05 PM
To: 'Nguyen, Melissa'
Subject: Follow-up on morphine sulfate injection pediatric issue

Hi Melissa,

I am so sorry about the confusion on the TC time today. The team decided to send the below to try to outline the situation on peds with the NDA and then if Hospira needs or wants to follow-up we can then go ahead and schedule a brief TC.

> We acknowledge your submission of a pediatric waiver request and literature review in NDA 202515 for morphine sulfate injection. Since approved versions of morphine sulfate exist for both IV (b) (4) injection and for the same proposed indication of your product, NDA 202515 does not trigger PREA, and therefore no pediatric studies are required for this NDA.
>
> However, if you wish to obtain pediatric labeling for your product, you must submit evidence of safety and efficacy in the proposed pediatric age groups for the proposed indication and routes of administration. This evidence may be based on studies conducted by you, studies you have reference to, or literature references. (b) (4)
>
> (b) (4)

Please let me know how Hospira would like to proceed after you have a chance to share and discuss this with your team.

Thanks, and again, my apologies for the confusion,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
301-796-1191
Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

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/s/

KIMBERLY A COMPTON
03/09/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202515

NDA ACKNOWLEDGMENT

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Product Manager, Regulatory Affairs

Dear Ms. Nguyen:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Morphine sulfate injection USP, 2, 4, 8, 10, 15, (b) (4) mg/mL

Date of Application: January 14, 2011

Date of Receipt: January 14, 2011

Our Reference Number: NDA 202515

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 15, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly A. Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KIMBERLY A COMPTON
01/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Pre IND 105936

MEETING MINUTES

Hospira, Inc.
275 N. Fields Drive
D-0389, Bldg. H2-2N
Lake Forest, IL 60045-5046

Attention: Melissa A. Nguyen
Manager, Global Regulatory Affairs

Dear Ms. Nguyen:

Please refer to your Pre-Investigational New Drug Application (PIND) file for morphine sulfate injection, USP.

We also refer to the meeting between representatives of your firm and the FDA on October 28, 2009. The purpose of the meeting was to discuss your proposed submission strategy and data requirements to support an application for your marketed but unapproved Morphine Sulfate Injection presentations, for the management of pain not responsive to non-narcotic analgesics.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

MEETING MINUTES

MEETING DATE: October 28, 2009

TIME: 3:00 PM

LOCATION: FDA White Oak Campus

APPLICATION: Pre IND 105936

STATUS OF APPLICATION: Pre-Submission

PRODUCT: Morphine Sulfate Injection, USP

INDICATION: management of pain not responsive to non-narcotic analgesics

SPONSOR: Hospira, Inc.

TYPE OF MEETING: B

MEETING CHAIR: Ellen Fields, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Christopher Hilfiger, Regulatory Project Manager

FDA Attendees	Title
Sharon Hertz, MD	Deputy Division Director
Ellen Fields, MD	Medical Team Leader
Tim Jiang, MD	Medical Officer
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
David Lee, PhD	Clinical Pharmacology Reviewer
Patricia Love, MD, MBA	Deputy, Office of Combination Products
Christopher Hilfiger	Regulatory Project Manager
Hospira Attendees	**Title**
Robert Bilkovski, MD, MBA	Associate Director, Medical Affairs
Francoix Gueffier	Technical Leader Research and Development
Edward Koo, PhD, DABT	Director, Pre-Clinical Development
Lee Reif	Senior Program Manager, Drug Development
Melissa A. Nguyen	Manager, Global Regulatory Affairs
Lisa Zboril	Director, Global Regulatory Affairs

BACKGROUND

Hospira, Inc. submitted a meeting request for a Type-B Pre-IND meeting on July 7, 2009. The company requested the Agency's input on the proposed submission strategy and data requirements to support an application for Morphine Sulfate Injection, USP.

Hospira currently markets multiple configurations of morphine products for the management of pain not responsive to non-narcotic analgesics. Hospira will also be proposing to include additional syringe configurations (iSecure®) with the NDA application which are not currently marketed (see attachment 1).

Question 1.

Does the Agency concur that a single 505(b)(2) submission is acceptable to register all of the proposed morphine product presentations

FDA Response:

This question requires additional internal discussion and will be addressed in the final meeting minutes as a post-meeting note.

Additional comments:

Please clarify the following:

1. **Whether the** (b) (4) **will be under your submission.**
2. **How the products in the** (b) (4) **will be delivered**
3. **Whether the** (b) (4) **morphine will be used for continuous infusion and if so, at what concentrations**
4. **Whether the** (b) (4)

Discussion:

The sponsor provided the following clarification:

(b) (4)

The Division confirmed that the sponsor must reference the pertinent DMFs in the NDA application. (b) (4) The sponsor responded that they are the holder of the container closure DMF and will provide a Letter of Authorization for the morphine sulfate drug substance DMF and any other DMFs referenced in the NDA submission.

The Division asked for clarification of the highest concentration they intend to market in the prefilled syringes and the sponsor stated that the highest concentration would be 15 mg/mL (see attachment 1).

(b) (4)

Question 2.

Does the Agency concur with Hospira's proposed product labeling strategy for the 505(b)(2) application for morphine products?

FDA Response:

You may support your proposed indication by reliance upon the Agency's finding of efficacy and safety for Duramorph (b) (4) and by reliance on published literature. An annotated label in PLR format must be submitted with the NDA that provides adequate support for all labeling language.

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf. **In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).**

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Final review of the labeling will occur at the time of NDA submission.

Discussion:

The Division stated that there have not been previously approved high concentration morphine injection solutions. Approval of the highest concentrations would require review of adequate preclinical and/or clinical data to assess the safety of the high concentrations. If adequate clinical data exists, this may preclude the need for preclinical data; however, this will need to be determined by the clinical review team. Additionally, the non-clinical sections of the label should be addressed at this stage of development. The Division stated that if the proposed dosing exceeds the referenced product dosing it must be justified by showing the relevance of existing data. If the dosing of the product does not exceed the referenced product, then this should be adequately described in the submission.

The sponsor responded that 80 – 90 % of morphine sulfate is used for acute pain and the remainder is used for the chronic pain. They added that clinicians are aware of how to properly dose morphine. The sponsor then stated that there are observational studies regarding dosing and that they intend to suggest a reduction in the current dosing except in rare cases where a higher concentration is needed.

The Division responded that the sponsor should examine the labeling of the product and that they will need to describe appropriate dosing instructions in the label submitted with the NDA. It is not necessary to establish a maximum daily dose since morphine is titrated based on individual patient response. It is not necessary to address chronic dosing or terminal end-of-life care in the label since this formulation is not intended for chronic use. Appropriate use in a continuous (b) (4) should be addressed in the label.

(b) (4)

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105936	GI-1	HOSPIRA INC	Morphine Sulfate Injection

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/s/

CHRISTOPHER M HILFIGER
12/08/2009