CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200403 SUPPL # HFD #

Trade Name Hydromorphone Hydrochloride Injection, USP

Generic Name

Applicant Name Hospira

Approval Date, If Known December 1, 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.

No studies. They received a biowaiver in lieu of relative BA studies.

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# 019034 Dilaudid (hydromorphone HCl) Injection, 1mg/mL, 2mg/mL, 4mg/mL, 10mg/mL, 250mg/vial

NDA#	019891	Dilaudid (hydromorphone HCL) Oral Solution, 5mg/5mL
NDA#	019892	Dilaudid (hydromorphone HCl) Tablet, 2, 4, 8 mg
NDA #	021217	Exalgo (hydromorphone HCl) ER Tablet, 8, 12, 16 mg

2. Combination product. Not a 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: Lisa Basham
Title: Senior Regulatory Health Project Manager
Date: 11/17/11

Name of Office/Division Director signing form: Sharon Hertz, M.D.
Title: Deputy Division Director

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/

LISA E BASHAM
12/01/2011

SHARON H HERTZ
12/01/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 200403 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Hydromorphone HCl Dosage Form: Injection		Applicant: Hospira Agent for Applicant (if applicable):
RPM: Lisa E. Basham		Division: DAAP

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)):

NDA 019034 Dilaudid

Provide a brief explanation of how this product is different from the listed drug.

The application proposes a formulation with different inactive ingredients than the listed drug relied-upon (Dilaudid): Hospira's proposed Hydromorphone Hydrochloride Injection, USP uses 60% sodium lactate solution and lactic acid as a buffer and sodium chloride for tonicity, whereas Dilaudid® (Purdue Pharma, L.P) uses 0.2% sodium citrate and 0.2% citric acid solution as a buffer.

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:

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	
• Proposed action • User Fee Goal Date is December 7, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None TA 2/25/11

[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.

❖ 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):

☐ 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:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ 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.
• 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? ☒ Yes ☐ No

  (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))).

  *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? ☒ Yes ☐ No

  (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**," 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 ***Hospira was sued by Purdue on October 8, 2010. The patent infringement suit was dismissed by a US district court (Illinois) on 6/27/11. The application is cleared for approval.***

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	Yes
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) TA: 2/25/11 AP: 12/1/11
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	Yes
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	No
• Original applicant-proposed labeling	No
• Example of class labeling, if applicable	Approved Dilaudid PI

[3] Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

❖ 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)*	Yes
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEPA ☐ DRISK ☒ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	Filing Review - 2/15/11 TA Action- 2/15/11 Cleared by committee 11/7/11 ☐ Not a (b)(2) 11/17/11
❖ 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 _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ 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

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	yes
❖ Internal memoranda, telecons, etc.	N/A
❖ 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
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ 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 1st cycle 2/25/11 2nd cycle 12/1/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None In the first cycle, it appeared that PMRs would be imposed once approved. However, with the second cycle review, Hospira addressed the issue adequately, thus no PMRs will be required.
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A-Deputy Director summary memo only
• Clinical review(s) *(indicate date for each review)*	N/A
• 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)*	no clinical studies
❖ 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 1/26/11

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

❖ 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
❖ 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 1/25/11
❖ 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 1/24/11 11/9/11(documenting no need for PMRs)
❖ 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 1/31/11
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 1/19/11 & 1/31/11 2nd cycle: 11/18/11
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 1/25/11
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None CMC Biopharm 10/25/10
❖ 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)*	Section II.B of 1/19/11 CMC review
☐ 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: 5/25/10 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ 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/

LISA E BASHAM
12/05/2011

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, November 15, 2011 12:58 PM
To: 'Hefele, Jennifer'
Subject: (b) (4) Inj. PI!!! (NDA 200403)
Attachments: PI sent to Hospira 9-15-11.doc

We made some relatively minor changes. Please confirm receipt and let me know what you think!

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
11/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403

ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE

Hospira, Inc.
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Attention: Jennifer Hefele, Ph.D., RAC
Program Manager, Global Regulatory Affairs

Dear: Ms. Hefele:

We acknowledge receipt on October 7, 2011, of your October 7, 2011, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We consider this a complete, class 1 response to our February 25, 2011, action letter. Therefore, the user fee goal date is December 7, 2011.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LISA E BASHAM
10/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hospira, Inc.
275 North Fields Dr.
Dept. 0389, Bldg H2-2
Lake Forest, IL 60045

Attention: Jennifer Hefele, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, 1, 2, and 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 Lisa Basham, Sr. Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
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
09/07/2011
on behalf of Parinda Jani

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, February 22, 2011 2:58 PM
To: 'Hefele, Jennifer'
Subject: FDA version of PI sent 2-22-11
Attachments: Draft PI sent to Hospira 2-22-11.doc

Back at ya! Only a few more minor changes.....

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
02/25/2011

Basham, Lisa

From: Basham, Lisa
Sent: Thursday, February 10, 2011 4:23 PM
To: 'Hefele, Jennifer'
Subject: PMRs for NDA 200403

Hi Jennifer,

Please find enclosed three post-marketing requirements that will be necessary in order to provide adequate qualification data for (b) (4) We note that these will not be necessary if you reduce the specification to NMT (b) (4); however, until the specification is reduced, we will require these Post-marketing studies. Propose dates for when you can reasonably but aggressively address these PMRs. If you are able to reduce the specification to NMT (b) (4) prior to completion of these studies, you can request that the agency release you from these PMRs.

Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug substance impurity identified as (b) (4) tested up to the limit dose for the assay.

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug substance impurity identified as (b) (4) tested up to the limit dose for the assay.

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Conduct a 3-month repeat-dose toxicology study in a single species with the isolated drug substance impurity identified as (b) (4)

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY

Please respond ASAP. Thank you!

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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/s/

LISA E BASHAM
02/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **INFORMATION REQUEST**

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

Attention: Jennifer Hefele, Ph. D.
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We are reviewing your carton and container labels submitted on January 27, 2011, and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

- Revise the font size for the text "Protect from light" on all labels to be all capital letters.

Please note that you only provided leachable results for 18-month real time stability samples. If in the future you seek shelf life extension, leachable results for longer stability points will be required.

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

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting 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
02/02/2011

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, February 08, 2011 5:45 PM
To: 'Hefele, Jennifer'
Subject: 2-8-11 draft package insert
Attachments: Draft PI sent to Hospira 2-8-11.doc

Hi Jennifer, Please see attached the draft package insert for NDA 200403. Please make sure that the Highlights section is consistent with the rest of the label (we didn't concentrate on the Highlights, although some things did make it into the Highlights during our edits). There are many changes from what you proposed. These changes would be consistent with a PLR conversion of the Dilaudid label (your RLD). Please make sure that the version that you send back to us ONLY shows differences from this version, i.e., accept all changes that you agree with and ONLY track deviations from this version. Please respond ASAP, as we will likely have additional changes once the label is cleaned up. Thanks!!

Lisa Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1175
email: lisa.basham@fda.hhs.gov

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LISA E BASHAM
02/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **DISCIPLINE REVIEW LETTER**

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

Attention: Jennifer Hefele, PhD
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your April 29, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

The Division of Medication Error Prevention and Analysis and the Office of New Drug Quality Assessment (CMC) have reviewed your proposed carton and container labels and has identified the following deficiencies:

1. We have identified postmarketing cases of confusion between the 2 mg/mL hydromorphone carpuject with both the 1 mg/mL hydromorphone carpuject and the 2 mg/mL lorazepam carpuject. Therefore, we request that you revise the font color of the established name and strength of the 2 mg/mL carpuject label so that the color provides more differentiation between the 1 mg/mL carpuject label (b) (4) and your lorazepam 2 mg/mL (b) (4) carpuject product. Additionally, you can further differentiate the labels and labeling for the 2 mg/mL hydromorphone carpuject labels by using a background color that highlights the established name and strength, boxing the strength in a different shape such as an oval instead of a rectangle, or other methods. Whichever color scheme is used to replace the (b) (4) for the 2 mg/mL hydromorphone carpuject should be carried across all your hydromorphone products that use the same (b) (4) for 2 mg/mL to remain consistent (e.g. the carton labeling of the 2 mg/mL hydromorphone carpujects, the container label and carton labeling for the isecure syringe for the 2 mg/mL strength, and the 2 mg/mL container label syringe for hydromorphone).

2. The images of the syringe container labels do not contain a bar code. Please ensure the bar code is included on the container labels for the 0.5 mg/mL, 1 mg/mL, and 2 mg/mL syringes in accordance with 21 CFR 201.25. 21 CFR 201.25 states:

Manufacturers, repackers, relabelers, and private label distributors of a human prescription drug product or an over-the-counter (OTC) drug product that is regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act are subject to these bar code requirements unless they are exempt from the registration and drug listing requirements in section 510 of the Federal Food, Drug, and Cosmetic Act.

3. Revise the presentation of strength on the container labels for the vial and ampules to be in accordance with United Stated Pharmacopeia's General Chapter <1> requirements which states:

   For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label.

   The current prominent presentation of strength states the total milligram content of the vial, but does not express the total volume. The presentation of strength on the container labels should follow the same presentation that you already use for the carton labeling. The concentration can be deleted since this information will be duplicative. The strengths should be listed as follows in the colored bar and be the only expression of strength on the container labels:

   1 mg/mL 2 mg/mL 4 mg/mL

4. (b) (4) . This similarity is contributing to confusion among the products. Thus, we recommend that you consider using a variety of colors for needle assemblies to help differentiate your products and strengths of the same product, particularly for those products and strengths that have been confused.

5. For all labels and packaging cartons, print the established name HYDROmorphone and the dosage form Injection in the same font and size for clarity and equal prominence.

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 Lisa E. Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
01/25/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, January 03, 2011 2:40 PM
To: 'Hefele, Jennifer'
Subject: RE: Information request for NDA 200,403- dated January 3, 2011

Hi Jennifer,
We are reviewing microbiology section of your NDA and request additional information as follows:

Please acknowledge the receipt.

Swati Patwardhan, MS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Phone (301)796-4085
Fax (301)796-9748

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/s/

SWATI A PATWARDHAN
01/03/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, December 17, 2010 7:48 AM
To: 'Hefele, Jennifer'
Subject: RE:Information request for NDA 200,403

Hello Ms. Hefele ,

We are reviewing microbiology section of your NDA and request additional information as follows.

1) In the filling sections of the executed batch records, (b) (4)

2) The batch records have an option of (b) (4) .

We are expecting the response by January 3, 2011. Could you let me know if this date is feasible at your end.

Let me know if you have any questions.

Thank you

Swati Patwardhan, MS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Phone (301)796-4085
Fax (301)796-9748

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/s/

SWATI A PATWARDHAN
12/17/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **INFORMATION REQUEST**

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

Attention: Jennifer Hefele, Ph. D.
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls and Toxicology 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.

- Following the review of your initial response to the 74-day letter, the Division requests that you provide the date you intend to submit the data regarding the further characterization of the structure of (b) (4) and available qualification data you may have that justifies exceeding the ICH Q3B(R2) qualification limits, if you can not tighten this specification to below the qualification threshold of (b) (4)

- Provide the approximate date you intend to submit the results of the leachable study on the container closure system and toxicological risk assessment for the identified leachables.

These data are necessary in order to complete the review of your NDA submission.

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

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting 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
12/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403

INFORMATION REQUEST

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

Attention: Jennifer Hefele, Ph. D.
Manager, Regulatory Affairs

Dear Dr. Hefele:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls 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. In your October 8th, 2010 Amendment, you stated that leachable studies will be executed on the product units currently under long term stability conditions and a report summarizing the results will be provided upon completion. Provide an estimated time that the data will be submitted. The leachable data is a critical component in your NDA's evaluation. We request that you provide the available data as soon as possible to facilitate our review.
2. Provide pH determination of the referenced approved drug Dilaudid® and comparison results to your hydromorphone hydrochloride injection product at two or more time points from date of manufacture.
3. Clarify if the [redacted] (b) (4) (Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls) have been subjected to the leachable study. Provide data to demonstrate and justify [redacted] (b) (4) If the data is already submitted, provide the correct reference.
4. In Section 3.2.P.5.3, Validation of Analytical Procedures – HPLC references Section 3.2.R Regional Information – Method Validation Package for the drug product HPLC analysis method validation report: This Methods Validation report cannot be located. Provide the correct reference or the report.

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting 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
11/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403 **INFORMATION REQUEST**

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

Attention: Pamela J. Riggio, MS
Regulatory Project Manager

Dear Ms. Riggio:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We are reviewing the Chemistry, Manufacturing and Controls 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. Clarify the regulatory status of the Carpuject cartridge and iSecure cartridge. Provide the name of the suppliers, a description, specifications, and Letter(s) of Authorization to pertinent Drug Master File(s) if applicable.
2. Provide placebo samples and example packaging cartons for each product packaging configuration.
3. Provide sufficient justification of the isotonicity of the drug product injection solution, e.g., calculation or experimental determination of osmolality.
4. Incorporate a separately prepared control standard in the drug substance/drug product analysis method to ensure correct preparation of the standard solutions.
5. Provide a description and validation of the assay and impurity analysis method, and GC method for residual solvents for the drug substance, as per ICH Q2B. Include example chromatograms for blank, standard and sample injections.
6. Provide the validation report for the drug substance assay and impurity method that includes peak purity data, as per ICHQ2B. Include accuracy results for (b) (4) or justify to the contrary.
7. Clarify the meaning of the numbers in Table 1 of Section 3.2.S.4.3, page 1, under each of the residual solvent columns. Provide a definition or unit for the numbers. Explain how the numbers support your conclusion of the PQL of all solvents by your definition of PQL in the paragraph above Table 1.

8. Section 3.2.P.5.3 references Section 3.2.R for a copy of the degradation product analysis method validation report, however, such report cannot be located. Provide the correct reference or the report.
9. Section 3.2.P.2.4 references Section 3.2.P.8 for a summary of extractable and leachable data, however, such data cannot be located. Provide the correct reference or the data.
10. Section 3.2.P.5.3, Validation of Analytical Procedures, Table 6, showed consistently (b) (4) for the 0.1 mg/mL formulation. Identify the source of the discrepancy between the 0.1 mg/mL and 0.2 mg/mL formulations.
11. When amending your NDA, clearly indicate sections and pages of the original NDA document that are being revised.

If you have any questions, call Swati Patwardhan, Regulatory Management Officer, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting 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
10/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403

FILING COMMUNICATION

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

Attention: Pamela J. Riggio, MS
Regulatory Project Manager

Dear Ms. Riggio:

Please refer to your new drug application (NDA) dated April 29, 2010, received April 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL.

We also refer to your submission dated June 25, 2010.

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 February 28, 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 February 7, 2011.

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

1. Your drug substance acceptance criteria for (b) (4) exceed the ICH Q3A(R2) qualification threshold of (b) (4) day, whichever is lower. You must either tighten these criteria to NMT (b) (4) % or provide

adequate safety qualification, which must include a minimal genetic toxicology screen (one in vitro assay for mutagenicity, one in vitro assay for DNA damage) and a repeat-dose toxicology study of 1 month duration to support the proposed specifications.

2. The current standard for potentially genotoxic impurities is to reduce the exposure to these impurities NMT [redacted] (b) (4) Provide your rationale, including discussions regarding technical feasibility, for the proposed specifications for [redacted] (b) (4)

3. Provide the structure and CAS number for [redacted] (b) (4) and indicate if it contains a structural alert for mutagenicity. If this impurity contains a structural alert, reduce the acceptance criteria to NMT [redacted] (b) (4) unless adequate justification is provided that this is not technically feasible. In addition provide the structure and CAS number for Impurities identified [redacted] (b) (4)

4. Given that [redacted] (b) (4) has been reported to test positive in carcinogenicity studies, reduce this impurity to NMT [redacted] (b) (4) or submit justification for the safety of the levels you have proposed, including supporting references. Such a safety assessment must take into consideration the maximum theoretical daily dose (MTDD) of hydromorphone via use of this product. To establish a MTDD, submit actual clinical use data for this or comparable products for review by the Division. [redacted] (b) (4) . Therefore, further justification for levels of [redacted] (b) (4) as an impurity, in this hydromorphone product, that exceed [redacted] (b) (4) will be required.

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

6. Provide photostability data for the drug product as per ICH Q1B.

7. You have provided an extractables assessment for the [redacted] (b) (4) closures for injections with no information on a leachables assessment in all of the proposed drug product packaging configurations. Provide adequate justification (including supportive data) for the absence of leachables in all of your proposed packaging configurations.

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.

If you have not already done so, you must 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. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional 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.

If you have any questions, call Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200403	ORIG-1	HOSPIRA INC	Hydromorphone Hydrochloride Injection 1,2,4 mg/mL

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/s/

SHARON H HERTZ
07/09/2010
Signing for Bob Rappaport, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200403

NDA ACKNOWLEDGMENT

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

Attention: Pamela J. Riggio, MS
Regulatory Project Manager

Dear Ms. Riggio:

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: Hydromorphone Hydrochloride Injection, USP, 1, 2, and 4 mg/mL

Date of Application: April 29, 2010

Date of Receipt: April 30, 2010

Our Reference Number: NDA 200403

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 June 29, 2010, 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) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, MS
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200403	ORIG-1	HOSPIRA INC	Hydromorphone Hydrochloride Injection 1,2,4 mg/mL

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/s/

LISA E BASHAM
05/12/2010