CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 200403 second cycle following TA action on February 25, 2011.

Name of Drug: Hydromorphone Hydrochloride Injection, 1 mg/mL, 2 mg/mL, and 4 mg/mL

Applicant: Hospira

Labeling Reviewed

Submission Date: Class 1 resubmission: Response to Tentative Approval.

Receipt Date: October 7, 2011

Background and Summary Description: Hospira received a tentative approval first cycle due to patent issues with Purdue Pharma, L.P., owner of the reference listed drug, Dilaudid. The case was dismissed with prejudice. The labeling was agreed upon first cycle. This review is a comparison of the agreed-upon labeling from the first cycle, and the labeling submitted in the Class 2 resubmission. The Sponsor made numerous formatting changes which are acceptable. Due to the complexity of the formatting changes, this reviewer is attaching a copy of the entire package insert compared with the last-cycle package insert using tracked changes.

Review

See attached label for differences between the agreed upon labeling from the first cycle and the submitted labeling this cycle. The CMC reviewer reviewed the submitted label and identified some additional changes to be made in the DOSAGE FORMS AND STRENGTHS section and the DESCRIPTION section as shown below:

(b) (4)

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

Recommendations

The above changes were sent to Hospira on November 15, 2011. Sponsor agreed with the changes on November 21, 2011 and corrected three typographical errors found in section 10. The agreed-upon label, submitted November 21, 2011, may be approved.

Regulatory Project Manager Date

Chief, Project Management Staff Date

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
11/22/2011

PARINDA JANI
11/22/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 200403 ***(second cycle following TA action)***	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Hydromorphone Hydrochloride Dosage Form: Injection Strengths: 1, 2, and 4 mg/mL		
Applicant: Hospira Inc.		
Date of Receipt: October 7 2011		
PDUFA Goal Date: December 7, 2011	Action Goal Date (if different): December 2, 2011	
Proposed Indication(s): management of pain in patients where an opioid analgesic is appropriate		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Dilaudid NDA 19034	The entire package insert

*each source of information should be listed on separate rows

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

No bridge: requested a waiver of BA/BE allowed under 21 CFR 320.22. Waiver granted.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

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

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

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

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

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

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Dilaudid	019034	Y

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

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

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

The application proposes a formulation with different inactive ingredients than the listed drug relied-upon (Dilaudid): Hospira's proposed Hydromorphone Hydrochloride Injection, USP uses (b) (4) ***and sodium chloride for tonicity, whereas Dilaudid® (Purdue Pharma, L.P) uses*** (b) (4)

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

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

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

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

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

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

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

YES ☒ NO ☐

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

YES ☒ NO ☐

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

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): 6589960

No patents listed ☐ *proceed to question #14*

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

YES ☒ NO ☐

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

Listed drug/Patent number(s): 6589960 (late-listed)

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

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

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

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

Patent number(s):

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

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

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

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

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

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

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

Patent number(s): 6,589,960
Method(s) of Use/Code(s):

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

(a) Patent number(s): 6,589,960
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

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

Date(s): **September 14, 2010**

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

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

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

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

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
11/17/2011

PARINDA JANI
11/17/2011

PMR/PMC Development Template

NDA 200403

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones*:

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

***Due to tentative approval (TA), milestone dates have not been established; however, the sponsor is still expected to conduct the study. Final dates will be updated upon approval, if these studies are not completed beforehand.**

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

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

The current drug substance specification for (b) (4) exceeds the ICH Q3A(R2) safety qualification threshold of NMT 0.15%. Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since this impurity is currently in an FDA approved generic drug product with a specification of NMT (b) (4). However, definitive safety qualification data does not exist. Should the required study demonstrate positive potential for mutagenicity, the specification will be reconsidered.

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

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

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

The study is an in vitro genetic toxicology study.

Required

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

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 200403

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones*:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

***Due to tentative approval (TA), milestone dates have not been established; however, the sponsor is still expected to conduct the study. Final dates will be updated upon approval, if these studies are not completed beforehand.**

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

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

The current drug substance specification for (b) (4) exceeds the ICH Q3A(R2) safety qualification threshold of NMT (b) (4). Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since this impurity is currently in an FDA approved generic drug product with a specification of NMT (b) (4) However, definitive safety qualification data does not exist. Should the required study demonstrate positive potential for mutagenicity, the specification will be reconsidered.

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

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

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 200403

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

PMR/PMC Schedule Milestones*:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

***Due to tentative approval (TA), milestone dates have not been established; however, the sponsor is still expected to conduct the study. Final dates will be updated upon approval, if these studies are not completed beforehand.**

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

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

The current drug substance specification for (b) (4) exceeds the ICH Q3A(R2) safety qualification threshold of NMT (b) (4) Safety qualification (minimal genetic toxicology screen and repeat-dose toxicology study) was deemed acceptable to be completed as a post-marketing requirement since this impurity is currently in an FDA approved generic drug product with a specification of NMT (b) (4) However, definitive safety qualification data does not exist. Should the required study demonstrate unacceptable general toxicity, the specification will be reconsidered.

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

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

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

This study is a repeat-dose toxicology study.

Required

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

Continuation of Question 4

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

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

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

/s/

KATHERINE S WON
02/25/2011

LAURA A GOVERNALE
02/25/2011
No milestone dates.

505(b)(2) ASSESSMENT

Application Information		
NDA # 200403	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Hydromorphone Hydrochloride Dosage Form: Injection Strengths: 1, 2, and 4 mg/mL		
Applicant: Hospira Inc.		
Date of Receipt: April 30, 2010		
PDUFA Goal Date: February 28, 2011	Action Goal Date (if different):	
Proposed Indication(s): management of pain in patients where an opioid analgesic is appropriate		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Dilaudid NDA 19034	The entire package insert

*each source of information should be listed on separate rows

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

No bridge: requested a waiver of BA/BE allowed under 21 CFR 320.22. Waiver granted.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

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

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

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

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

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

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Dilaudid	019034	Y

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

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

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

The application proposes a formulation with different inactive ingredients than the listed drug relied-upon (Dilaudid): Hospira's proposed Hydromorphone Hydrochloride Injection, USP uses (b) (4) ***and sodium chloride for tonicity, whereas Dilaudid® (Purdue Pharma, L.P) uses*** (b) (4)

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

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

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

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

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

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

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

YES ☒ NO ☐

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

YES ☒ NO ☐

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

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): 6589960

No patents listed ☐ *proceed to question #14*

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

YES ☒ NO ☐

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

Listed drug/Patent number(s): 6589960 (late-listed)

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

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

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

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

Patent number(s):

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

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

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

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

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

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

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

Patent number(s): 6,589,960
Method(s) of Use/Code(s):

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

(a) Patent number(s): 6,589,960
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

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

Date(s): **September 14, 2010**

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

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

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

Hospira was sued by Purdue on October 8, 2010.

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
02/25/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200403 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Hydromorphone Hydrochloride Dosage Form: Injection Strengths: 1, 2, 4 mg/mL		
Applicant: Hospira Inc. Agent for Applicant (if applicable): N/A		
Date of Application: April 29, 2010 Date of Receipt: April 30, 2010 Date clock started after UN:		
PDUFA Goal Date: February 28, 2011	Action Goal Date (if different):	
Filing Date: June 29, 2010	Date of Filing Meeting: June 8, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed indication: management of pain in patients where an opioid analgesic is appropriate		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

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

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* 5/13/10		**X**		**Schedule II**
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*			X	There are no clinical or BA/BE studies
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?			X	
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	Electronic submission

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 8, 2010

BLA/NDA/Supp #: 200403

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Hydromorphone Hydrochloride

DOSAGE FORM/STRENGTH: Injection, 1, 2, and 4 mg/mL

APPLICANT: Hospira Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of pain in patients where an opioid analgesic is appropriate

BACKGROUND: 505(b)(2) to Dilaudid NDA 019034

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical :Sharon Hertz will sign off on the application. No primary clinical review or CDTL review.	Reviewer:	No primary clinical reviewer	Y (Dr. Hertz)
	TL:		
~~Social Scientist Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OTC Labeling Review (*for OTC products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Clinical Microbiology (*for antimicrobial products*)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———

Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Suresh Doddapaneni	N
~~Biostatistics~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Belinda Hayes	N
	TL:	Dan Mellon	Y
~~Statistics (carcinogenicity)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
Product Quality (CMC)	Reviewer:	Xiaobin Shen	N - Danae covered
	TL:	Presad Peri	N
Quality Microbiology *(for sterile products)*	Reviewer:	Denise Miller	Y
	TL:		N
CMC Biopharm Review (Patrick Marroum/Angelica Dorantes?)	Reviewer:	Angelica Dorantes	Y
	TL:	Patrick Marroum	N
Facility Review/Inspection	Reviewer:		N
	TL:		N
~~OSE/DMEPA (proprietary name)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~OSE/DRISK (REMS)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———
~~Bioresearch Monitoring (DSI)~~	~~Reviewer:~~	———	———
	~~TL:~~	———	———

Other reviewers	CSS: JP Gong/Lori Love OSE:	N
Other attendees		

FILING MEETING DISCUSSION:

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

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Risk assessment to justify impurity levels. Make sue as low as technically feasible	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No leachable/extractable assessment or inverted configuration stability data	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
CMC Biopharm Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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/s/

LISA E BASHAM
02/15/2011

PARINDA JANI
02/15/2011

MEMORANDUM

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

Date: January 26, 2010

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

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

From: JianPing (John) Gong, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Consultation on Hydromorphone HCl Injection

NDA #:	200-403
Indication:	Management of pain where an opioid is appropriate
Strengths:	1, 2, and 4 mg/mL
Sponsor:	Hospira, Inc
Document Date:	April 29, 2010
PDUFA Goal Date:	February 28, 2011

Background

The Division of Anesthesia and Analgesia Products (DAAP) consulted the Controlled Substance Staff (CSS) regarding the abuse potential of Hydromorphone HCl Injection. This NDA is for (b) (4) unapproved drug.

This product contains the same dosage form and active ingredient at the same concentrations as the Reference Listed Drug (RLD), Dilaudid®, and is intended for intravenous, subcutaneous or intramuscular administration.

Hydromorphone is a semisynthetic 5-ring morphinan derivative opioid analgesic with effects similar to those of morphine. Interaction with the μ-opioid receptor subtype is responsible for most of the clinical effects of hydromorphone.

CSS Comments

There are no preclinical and clinical abuse potential studies in the NDA submission. The Sponsor is not seeking any claims or labeling statements regarding abuse deterrence or abuse resistance of the formulation.

Hydromorphone is a CII substance under Controlled Substances Act (CSA) and is historically associated with high levels of abuse. Therefore, CSS reminds the Sponsor to store and handle the product consistently with regulations for Schedule II narcotic drugs

by storing in a securely locked, substantially constructed cabinet or enclosure with limited access to prevent theft or diversion into illegal channels of distribution.

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/s/

Jianping P GONG
01/26/2011

MICHAEL KLEIN
01/26/2011

MEMORANDUM

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

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

Date: January 28, 2011

To: Lisa Basham – Senior Regulatory Health Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

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

CC: Lisa Hubbard – Professional Group Leader
Shefali Doshi – DTC Group Leader
Twyla Thompson – Regulatory Review Officer
DDMAC

Subject: **DDMAC draft labeling comments**
NDA 200403 hydromorphone hydrochloride Injection C-II

DDMAC has reviewed the proposed product labeling (PI) for hydromorphone hydrochloride Injection C-II submitted for DDMAC review on January 19, 2011.

The following comments are provided using the proposed PI sent via email on January 27, 2011, by Lisa Basham. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

MATHILDA K FIENKENG
01/28/2011

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

Date:	January 13, 2011
Application Type/Number:	NDA 200403
To:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products
Through:	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	HYDROmorphone Injection 1 mg/mL, 2 mg/mL, and 4 mg/mL
Applicant:	Hospira
OSE RCM #:	2010-1048

EEXECUTIVE SUMMARY

This review evaluates the proposed labels and labeling for Hospira's hydromorphone product line.

Our evaluation found the 2 mg/mL carpuject container label is similar to the 1 mg/mL carpuject container label. This similarity has lead to a selection error that resulted in an overdose. Additionally, the 2 mg/mL carpuject label for hydromorphone has also been confused with the container label for Hospira's lorazepam 2 mg/mL carpuject syringe. As such, the labels need to be revised prior to approval. We have provided recommendations for the container labels to help minimize confusion of these products and to revise the labels and labeling to include required information on the labels and labeling in Section 5.1.

1 INTRODUCTION

This review responds to a request from the Division of Anesthesia and Analgesic Products (DAAP) for DMEPA's evaluation of the proposed container label, carton and insert labeling for vulnerabilities that might lead to medication error with the proposed Hospira Hydromorphone product line. This application is a 505(b)2 of Dilaudid (NDA 019034) and is not a generic due to the different excipients found in this NDA.

2 METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database for medication errors specifically related to Hydromorphone Injection marketed by Hospira. Reports excluded from evaluation include those that described adverse events not related to medication errors, reports that did not included Hospira's Hydromorphone products (reports involving other manufactures), and reports that did not involve a medication error associated with Hydromorphone.

Reports describing a medication error were screened for duplicates and combined into cases. The medication error cases were categorized by type of error and evaluated for root causes and contributing factors that led to the error.

Additionally, DMEPA evaluates the proposed container label, carton and insert labeling for areas that may have contributed to the postmarketing errors and reviewed the labels and labeling for other areas that may contribute to confusion and error. DMEPA also compares the proposed labels and labeling to Dilaudid, the RLD for this product.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

DMEPA performed an AERS search on November 4, 2010 using the following criteria: active ingredient "Hydromorphone%" and the verbatim term "hydromor%"; and the MedDRA reactions "Medication Errors NEC" (HLT), "Medication Monitoring Errors" (HLT), "Product Label Issues" (HLT), "Product Package Issues" (HLT), "Inappropriate Schedule of Drug Administration" (PT), "Wrong Drug Administered" (PT), "Underdose" (PT), "Drug Dose Omission" (PT), "Drug Administration Error" (PT), "Incorrect Route of Drug Administration" (PT), "Incorrect Drug Administration Rate" (PT), "Incorrect Drug Administration Duration" (PT), "Wrong Technique in Drug Usage Process" (PT), "Incorrect Dose Administration" (PT), "Intercepted Drug Administration Error" (PT), "Accidental Exposure" (PT), "Drug Exposure Via Breast Milk" (PT), "Accidental Drug Intake by Child" (PT), "Accidental Overdose" (PT), "Overdose" (PT), "Multiple Drug Overdose" (PT), "Multiple Drug Overdose Accidental" (PT), "Drug Administered at Inappropriate site" (PT), "Drug Administration Error" (PT), "Incorrect Drug Dosage Form Administered" (PT), and "Incorrect Dose Administered" (PT).

DMEPA then conducted a text search of each case including the narrative, and all searchable fields for the word "Hospira".

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) uses the principal of human factors, Failure Mode and Effects Analysis[1] (FMEA) and lessons learned from postmarketing experience to evaluate the proposed container labels (see Appendix A) and carton (see Appendix B) submitted on April 30, 2010. Additionally, DMEPA compared the proposed labels and labeling to the RLD, Dilaudid (see Appendix C).

3 RESULTS

The following summarizes our findings from the AERS search and review of the proposed container labels, carton and package insert labeling.

3.1 AERS RESULTS

The AERS search retrieved a total of 344 reports. Twenty-nine cases remained after eliminating the reports that did not specify a Hospira Hydromorphone product as outlined in section 2 (see Appendix F). After applying the remainder of the exclusion criteria stated in section 2, three cases remained (these cases are highlighted yellow in Appendix F).

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

All three cases describe confusion related to the container labels of the carpuject products. One case (ISR #5519003) describes confusion between the 1 mg/mL and 2 mg/mL strengths of hydromorphone. (b) (4) . These similarities contributed to a selection error that lead to an overdose of a patient. The nurse intended to administer a 1 mg dose of hydromorphone, however the nurse removed the 2 mg/mL strength. Patient outcome was not reported.

The remaining two cases described confusion between different products within Hospira's carpuject product line. The first case (ISR #5640736) describes confusion between hydromorphone and lorazepam. Lorazepam is marketed by Hospira in vials, isecure syringes, and carpuject syringes. Lorazepam is available in the same strength (2 mg/mL) and packaging configuration as Hydromorphone (b) (4) and described two patients receiving the wrong medication (Lorazepam instead of Hydromorphone) prior to the error being discovered. The cases stated that the patients did not have any serious adverse events due to the medication errors.

The remaining case (ISR 5519033) describes a complaint that all carpuject products look similar. Hospira markets 25 different products in the carpuject closure system (see Appendix E). Three products (Lorazepam, Morphine, and Midazolam) share an overlapping strength with hydromorphone. DMEPA evaluated the container label for these three products to ensure that the products are well differentiated to minimize the possibility or wrong drug errors.

3.2 Labels and Labeling

Our evaluation of the proposed container labels, carton and package insert labeling noted that Hospira proposed to tallman "HYDRO" in hydromorphone on the proposed labels and labeling. We find this proposal acceptable because it will help differentiate this established name from morphine. We also find the use of the capital "HYDRO" acceptable because the Institute for Safe Medication Practices conducted a survey of 1,125 subscribers and found that 67% were in favor of capitalizing these letters to prevent medication errors[2].

Additionally, we found that the carpuject syringes are vulnerable to confusion and lead to medication errors. This confusion can occur between the different strengths of hydromorphone or different products that also use the carpuject delivery system. This confusion is due to the container closure systems (b) (4) . In addition to similar container closure systems and similar color schemes overlapping strengths also exist. Additionally, other improvements can be made to the proposed labels and labeling to avoid duplication, remove unnecessary information, and to include required information on the labels and labeling.

4 DISCUSSION

Our evaluation noted similarities with the container closure system, container labels of the carpuject syringe that increased the similarities of products using the carpuject system that have contributed to medication error with this product and other Hospira products.

[2] Hydromorphone Survey; Acute Care Newsletter; Institute for Safe Medication Practices, August 23, 2007.

There are three other products within the Hospira product line that share an overlapping strength with hydromorphone carpujects. To minimize the confusion reported postmarketing with these products it will be important to differentiate the strengths for the carpuject labels in the Hospira line.

5 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation finds that the container labels of the 2 mg/mL hydromorphone carpuject syringes are similar to the 1 mg/mL hydromorphone carpuject syringes and lorazepam 2 mg/mL carpuject syringes. This similarity has contributed to medication errors. Thus, we recommend revising the 2 mg/mL hydromorphone container labels to minimize confusion between these products. Additionally, improvements can be made to the labels and labeling to avoid duplicative information, remove unnecessary information that clutters the label, and include required information. In section 5.1 DMEPA provides recommendations for the container labels and carton labeling for the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Abolade Adelou, OSE project manager, at 301-796-4264.

5.1 COMMENTS TO THE APPLICANT

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

6 REFERENCES

1. Adverse Events Reporting System (AERS)

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

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APPENDIX F

Case Numbers and Narratives

Case Numbers	Narratives
4741879	Report from the USA of over sedated and over delivery coincident with HYDROMORPHONE HYDROCHLORIDE therapy. On an unspecified date in 2004, the patient was post operatively recovering from an unspecified orthopedic surgical procedure and received an unreported amount of HYDROMORPHONE HYDROCHLORIDE via a patient control analgesia (PCA) pump for an unspecified indication and became over sedated due to an over delivery. The reporter stated that a nurse witnessed a family member pushing the patient pendant on the PCA while the patient was sleeping in addition to witnessing the patient initiate their own deliveries when awake resulting in the patient becoming over sedated. The specific PCA parameters were unknown. The patient was treated with NARCAN and recovered without sequelae. The reporter's opinion of causality between the events and HYDROMORPHONE HYDROCHLORIDE was not reported.
4604825	Report from the usn of unresponsive, not breathing, medication error, and overdose coincident with HYDROMORPHONE (DILAUDID) therapy. In Aug 7004, the patient was hospitalized for minor gastrointestinal surgery. In Aug 2004, the pharmacist miscalculated the patient's DILnUDID order. The order called for DILAUDID 20 mcg/ml to be mixed and infused at 8 ml/hr with titration. Instead of making a DILAUDID infusion of 5 mg/250 ml, the· pharmacist made a 50 mg/250 ml bag, which resulted in a 200 mcg/ml concentratIon, which was given to the patient. The patient was found to be unresponsive and not breathing, and was resuscitated and placed on life support. The patient died the following day. The reporting healthcare professional believed the DILAU~ID possib!y contributed to 9r resulted In the patlent's death. It IS unknown if DILAUDID was the only contributing factor in the patient's death.
5097645	Literature report from the USA of severe dyspnea and wrong dose administered coincident with HYDROMORPHONE HYDROCHLORIDE (HYDROMORPHONE HCL); dyspnea coincident with FENTANYL CITRATE (FENTANYL), MEPERIDINE HYDROCHLORIDE (DEMEROL), HYDROMORPHONE HCL and MORPHINE SULFATE; pruritus and urticaria coincident with FENTANYL, DEMEROL, HYDROMORPHONE HCL and MORPHINE SULFATE; and condition aggravated coincident with FENTANYL therapy. The

	purpose of this article was to present a patient with Opioid intolerance who was not able to be treated by standard methods yet required multiple major surgeries and Opioids for postoperative pain control. This patient received FENTANYL, HYDROMORPHONE HCL, DEMEROL and MORPHINE SULFATE for postoperative pain management and experienced pruritus and urticaria with occasional occurrence of dyspnea. These reactions occurred within minutes of the administration of the Opioid and recurred each time a dose was administered. The reactions continued when other potential causative agents, such as Anti-emetics and postoperative Antimicrobials given during the same time frame were withheld. The patient was then transitioned to Oral OXYCODONE, CODEINE, and PROPOXYPHENE. She also developed symptoms with all the Opioids administered. Antihistamine therapy, given concomitantly with the Opioids, led to decreased severity of the pruritus and urticaria. She was admitted to the neurological service for shunt revision. She received escalating doses of FENTANYL and developed fleeting urticarial lesions and generalized pruritus. HYDROXYZINE was given as treatment and the patient improved. The operation was successfully completed. Postoperatively, she received bolus doses of FENTANYL which led to worsening of pruritus, urticaria, and mild dyspnea without wheezing. The addition of regularly scheduled DIPHENHYDRAMINE improved the patient's pruritus and urticaria. She was discharged home with transdermal FENTANYL, ACETAMINOPHEN and HYDROXYZINE. She reported pruritus and intermittent, mild urticaria with the use of the transdermal FENTANYL patch in association with scheduled HYDROXYZINE. Three months later, she was readmitted for another shunt revision. The patient tolerated as much as 1 mg of oral HYDROMORPHONE HCL with the development of generalized pruritus but with no urticaria or dyspnea. She received a continuous HYDROMORPHONE HCL infusion. The operation was again successful but she inadvertently received a bolus dose of HYDROMORPHONE HCL in the post anesthesia care unit in addition to continuous infusion. She experienced severe dyspnea and EPINEPHRINE was given as treatment. No further bolus doses were administered after this event. The patient's pain was well controlled by increasing the infusion rate of HYDROMORPHONE HCL with the addition of ACETAMINOPHEN. The patient has since been readmitted for repeat neurosurgical procedures and has been placed immediately on continuous HYDROMORPHONE HCL infusion. Good pain control with this regimen has been achieved. The patient did not develop significant adverse events. The author stated, "Beginning at 15 years of age, the patient began developing adverse reaction to Opioids used for postoperative pain management. These reactions were similar regardless of the Opioid administered and consistently manifested as prutitus and urticaria to Opioids administered intravenously (FENTANYL, HYDROMORPHONE, MEPERIDINE, and MORPHINE)." The author also cited the following statements as attributions: "The patient was given escalating doses of FENTANYL intravenously in an attempt to determine a highest tolerated dose {Table I). The patient developed fleeting urticarial lesions and generalized pruritus."; "The operation was successfully completed, but inspite of increasing the rate of FENTANYL infusion, bolus doses were required for pain control postoperatively, which led to worsening pruritus, urticaria, and mild dyspnea without wheezing."; and "The operation was once again successfully completed,but the patient was inadvertently administered a bolus dose of 1 mg HYDROMORPHONE in the postanesthesia care unit in addition to the continuous infusion. This led to severe dyspnea requiring the administration of EPINEPHRINE intramuscularly." The following drugs were also considered suspects for the following events: Anti-emetic, Antimicrobial,

	OXYCODONE, CODEINE and PROPOXYPHENE for urticaria, dyspnea, and pruritus; Oral HYDROMORPHONE for generalized pruritus; and Transdermal FENTANYL patch for pruritus and urticaria.
4929710	Report from the USA of respiratory distress, apnea, overdose and medication error coincident with HYDROMORPHONE HYDROCHLORIDE therapy. On (b) (6) a patient in the post anesthesia care unit received a loading dose of 22mL of HYDROMORPHONE HYDROCHLORIDE instead of the intended loading dose of 2mL. The patient experienced apnea and respiratory distress and was treated with one dose of NARCAN. The patient's outcome and reporter's opinion of causality were not reported
4943529	Literature report from the USA of suicide and overdose coincident with HYDROMORPHONE HYDROCHLORIDE (HYDROMORPHONE HCL) therapy. The purpose of this article was to report suicides by apparent motor vehicle-related CARBON MONOXIDE (CO) poisoning and high concentrations of concomitant prescription drugs. This is the 11th of 19 reports from the same article. The patient died of CO poisoning. Upon autopsy, toxicological analysis was positive for HYDROMORPHONE HCL. The manner was suicide. The author cited the adverse events in Table III entitled, "Incidence and Frequency of Drug and Ethanol Findings in CO Suicide Case Population (Excluding NICOTINE and CAFFEINE)." The author also attributed the events to the drugs as stated in the title, "Apparent Suicidal CARBON MONOXIDE Poisoning with Concomitant Prescription Drug Overdoses". The referenced literature article for this case resides with case file # 06H-163-0305963-00. ********** Autopsy Results: Positive for HYDROMORPHONE HYDROCHLORIDE
5835154	Report from the USA of too much medication coincident with HYDROMORPHONE HYDROCHLORIDE INJECTION (HYDROMORPHONE HCL INJECTION) therapy. On (b) (6), the patient received HYDROMORPHONE HCL INJECTION for post operative pain after a total knee replacement and experienced received too much medication. It was reported that the nurse programmed the pump to deliver medication with a 0.1mg/ml concentration instead of the intended 1.0mg/ml. Treatment included intravenous NARCAN and the patient recovered. The reporter believed the events were probably related to the HYDROMORPHONE HCL INJECTION.
5835157	Report from the USA of non responsive coincident with HYDROMORPHONE HYDROCHLORIDE INJECTION (HYDROMORPHONE HCL INJECTION) therapy. On 22 December 2007, the patient received HYDROMORPHONE HCL INJECTION for an unknown indication and experienced non responsiveness. It was reported that the PCA pump "delivered 9ml during the 20 minutes that the pump was running". The patient was treated with two doses of 0.4 mg f NARCAN intravenously and recovered. The reporter's opinion of causality was not reported. COMPANY CAUSALITY:

	Non responsive: Possible Medication error: possible
5592662	Report from the USA of hypoxic brain injury, stopped breathing, asystole, and received more medication than intended coincident with Hydromorphone Hydrochloride (Hydromorphone HCL Injection) therapy. On (b) (6) , a patient was admitted to a long-term care facility for acute pain prior to a scheduled hip replacement and experienced hypoxic brain injury, stopped breathing, asystole, and received more medication than intended. The pump was programmed on (b) (6) at 2040 to deliver Hydromorphone HCL Injection with a concentration of 3mg/ml in the PCA continuous mode, a 0.5 mg PCA dose, a 30 minute patient lockout, with no one hour or four hour limit. On (b) (6) at 0000, the vial was changed and the delivery was resumed. At approximately 0600, the pump was alarming and the nurse went to check on the patient and noticed the vial was empty. "She noted the patient was breathing, but not properly. The nurse repositioned the patient and the patient stopped breathing." A code was called and the patient was noted to be in asystole. The patient was intubated and Atropine and Epinephrine were given, amount and route not reported. Within 10 minutes, the patient was in normal sinus rhythm and the patient's vital signs were responding. The patient was transferred to the Intensive Care Unit (ICU), had a feeding tube inserted and a tracheotomy performed. The patient remains in ICU on a ventilator, responsive only to deep pain with no purposeful movements. The reporter stated "the patient sustained a hypoxic brain injury with some permanent sequelae. When the syringe was changed, either the nurse did not catch that the concentration of the new syringe was different or the pump was reprogrammed incorrectly. The patient was to receive a maximum of 9 mg in six hours but received 30 mg in six hours." The reporter believed the events were probably related to the Hydromorphone HCL Injection. Company Causality: Hypoxic brain injury: User error in programming of the infusion pump Stopped breathing: User error in programming of the infusion pump Asystole: User error in programming of the infusion pump Received more medication than intended: User error in programming of the infusion pump Medication error: User error in programming of the infusion pump
5103058	Hydromorphone. Canada. Hydromorphone intoxication. Ser. Lit. 41M. 3 of 19. This medically significant literature report received from Canada describes a 41-year-old male subject, who received hydromorphone and experienced hydromorphone intoxication. Medical history and concomitant medications not provided. On an unknown date, the subject started to receive hydromorphone (route, dose unknown) for drug abuse. On an unknown date the subject was found dead in the fetal position.. There was a puncture mark in the left antecubital fossa. Intravenous drug paraphernalia and numerous drugs were at the site. The subject's right lung was slightly congested. The subject's heart blood concentration of hydromorphone was 141 ng/ml. The manner of death was accidental. Cause of death was hydromorphone intoxication. Company medical Assessment (1-Sep-06): Hydromorphone intoxication is not due to the drug itself. This is either related to improper dosing or drug abuse/misuse. Company Causality (1-Sep-06): Not related Wallage, H.R., Palmentier, J-P.F.P. et al. Hydromorphone-Related Fatalities in Ontario. Journal of analytical toxicology. Apr 2006. 30(3): 202-9
6493341	Literature report from the USA describing a case of fatal drug interaction, fatal aspiration, fatal inappropriate device programming, fatal overdose and fatal respiratory arrest. This is the sixth of seven reports from the same article. The referenced literature article resides with case tile 111319.

	Case number 7 (79 years old, gender not reported) received hydromorphone (0.75 mg/day, intrathecal) and bupivacaine (0.9 mg/d, intrathecal) for noncancer pain on an unknown date between (b) (6). Past medical history and concomitant medications were not reported. The patient had chronic obstructive pulmonary disease and asbestosis. The patient underwent placement of the intrathecal opioid pump (pump flow rate 0.966 ml/d of hydromorphone 15 mg/ml and bupivacaine 18 mg/ml; programmed morphine-equivalent dose 2.25-4.5 mg/d). The patient's opioid-related risk factors included: age, chronic obstructive pulmonary disease (COPD) and asbestosis. Within 1 day of placement of the intrathecal opioid pump, while the patient was in the emergency room, the patient experienced overdose, aspiration and respiratory arrest. It was not reported if prodromal symptoms of overdose (lethargy, drowsiness, somnolence, respiratory depression, apneic periods and/or snoring) were present. Treatment of the adverse event was not reported. The patient died on an unknown date, causes of death were drug interaction, aspiration, inappropriate ' device programming, overdose, and respiratory arrest. It was not reported if an autopsy was performed. The author cited the adverse events in Table 2 titled, "Summary of Nine index Cases of Death within 3 Days after Intrathecal Opioid Device Implant". The author stated, "These findings were consistent with the nine index cases that revealed respiratory arrest caused or contributed to death in all patients." The author also stated, "Errors in dosage calculations or pump programming caused or contributed to two deaths (cases 7 and 9)." The author further stated, "Respiratory depression as a consequence of intrathecal drug overdosage or mixed intrathecal and systemic drug interactions is one plausible, but hypothetical mechanism." The patient's age, COPD and asbestosis were cited as contributing factors. Coffey R.J., et al. Mortality Associated with Implantation and Management of Intrathecal Opioid Drug Infusion Systems to Treat Noncancer Pain. Anesthesiology. -Oct-2009. 111(4): 881-891. Company Causality (04 December 2009): Possible
6645717	Spontaneous report from the USA describing a case of respiratory arrest. This is the third of four reports from the same facility. A health care professional reported that a 45 year old male patient, received hydromorphone hydrochloride (PLOTS 85570LL, 84575LL or 83595LL) 1 mg, intravenous (IV), twice and 2 mg, IV, once, (total dosage of 4 mg) for an unknown indication on 26 Jan 2010. The patient's medical history includes achalasia, GERD, obesity and severe abdominal pain. Concomitant medications include ondansetron 4 mg, IV, once, for an unknown indication. On 26 Jan 2010, after a total dosage of 4 mg of hydromorphone hydrochloride was administered, the patient experienced respiratory arrest. The patient received 1 mg of hydromorphone hydrochloride at 23:16 and 1 mg at 23:36; an additional 2 mg was administered at 23:50. After he had received a total of 4 mg of hydromorphone hydrochloride the patient went into respiratory arrest. Laboratory tests and diagnostic procedures were not reported. Treatment included CPR and Naloxone 1 mg IV once and the patient recovered. The reporter considered the event as probably related to the hydromorphone hydrochloride. Overall case causality: Possible. Temporally related and on the spectrum of sequelae from labeled events, consider contributory effects of dosing technique, baseline respiratory function and short administration time frame for this seemingly high dose of drug delivery.
6751543	Spontaneous report from the USA describing a case of unresponsive and thready pulse. A healthcare professional reported that a 58 year old male patient received hydromorphone

	(lot unknown) IV (intravenous route) starting on 06 Mar 2010 via a PCA device programmed to deliver 1mg/mL with a 0.8mg loading dose, in the PCA+continuous mode, at a continuous rate of 0.1mg/hr, a 0.3mg PCA dose, a 10 minute patient lockout, and a lhour 1.1mg dose limit. The patient's medical history and concomitant medications were not reported. On 07 Mar 2010, while receiving hydromorphone a patient experienced unresponsive and thready pulse. The patient was admitted through the Emergency Room (ER) on (b) (6) for hard coughing with headaches and to rule out a cerebral bleed. On (b) (6), at 2040, the patient underwent an MRI of the head which was reported as an "unremarkable exam." On (b) (6) at 2214, the patient's vital signs were heart rate (HR): 78, Blood pressure (BP) 111/74, respirations 18, and (oxygen) 02 saturation 95%. The physician ordered a PCA for pain control and the patient was admitted to a medical-surgical unit. On (b) (6) at 2240, the PCA was programmed, two nurses checked the programming, and the delivery was started. On (b) (6) at 0254, it was reported that the patient's vital signs were HR 100, BP 114/68, respirations 18, and 02 saturation 90%. At 0433, during nursing rounds, the patient was found in bed with "snoring respirations but was unresponsive." At this time it was noted that the patient had a "thready pulse". The patient's vital signs at this time were reported as BP 100/61 and an 02 saturation of 23. The delivery was stopped and a code was called. No CPR was performed, but 02 was administered at 100% via an ambu bag. The patient was intubated and treated with 2 doses of Narcan; One dose of 0.4mg, route not reported, was administered, but the patient did not respond until the second unknown dose of Narcan was administered at 0550. At 0520, the patient's vital signs were reported as HR 114, BP 97/57, respirations 14, with an 02 saturation of 99% At 0651, a Narcan drip (2mg/500mL) at a rate of 100mL/hr was started. The patient was then transferred to the Intensive Care Unit (ICU). At 0730, the patient's 02 saturation was 97%, and at 0745 it was 93%. An Arterial Blood Gas (ABG) performed at 0740 indicated an arterial 02 saturation of 95%. The patient was reportedly extubated "within four hours of the event.", and PCA therapy was not resumed. The event did not prolong the patient's hospitalization. The patient was considered recovered on 07 Mar 2010; a physician's exam found no deficits. The patient did remain in the hospital in the attempt to determine the etiology of his headaches and was discharged to home on (b) (6) The reporter's opinion of causality was "unsure" at this time with respect to the events and the hydromorphone therapy. 06 Apr 2010: New information received regarding events. Spontaneous report from the USA describing a case of unresponsive, thready pulse, and programming error. The reporter stated that the event was due to a "programming error by the nurse in programming the concentration at 0.1mg/mL instead of 1mg/mL." Overall case causality: Possible Temporally related and on the spectrum of labeled events or their sequela, consider contributory effect of concomitant medication, presenting illness, unknown baseline, dosing schedule and overall doses that are seemingly generous given history; thready pulse is a highly sugbective and poorly qualified term.
6015187	Pt. was originally ordered PCA hydromorphone 1mg/ml, order changed to a higher concentration of 5 mg/ml. New cartridge loaded, pump settings were not changed. Pt was found unresponsive & could not be resucitated. medication error
5523406	Morphine and hydromorphone carpuject look almost the same and are subject to error all carpujects look similar such as metoclopramide, dolasetron, diphenhydramine etc...

	Unknown Morphine and hydromorphone carpuject look almost the same and are subject to error all carpujects look similar such as metoclopramide, dolasetron, diphenhydramine etc...
4585476	we currently are using hydromorphone distributed by faulding pharmaceutical/mayne pharma. labels on vials are confusing to users. Label stated "hydromorphone 2 mg/1ml" "2ml vial". the vial only contains 1ml of solution. explanation from mayne pharma is that the "2ml vial" refers to the total capacity of the vial not the total contents. i have a letter from the company stating they are in the process of revising the label. this has caused concern from nursers when they are only able to draw 1ml of solution from the vial. two nurses called the pharmacy on 2 separate occasions. the medication was in our automated dispensing cabinet described as labeled 2mg/1ml 2ml vial.
5142120	PCA pump was programmed wrong and patient received 300 mg IV Dilaudid over 2 hour period. Original PCA order was handwritten on a physician order form-preprinted PCA Order Sheet was not utilized. This was a custom made vial of Dilaudid made per hospital Pharmacy. Pharmacy label was confusing in relation to the dilution and in fact the pharmacist mixed this vial with a different concentration than usual. Nurse hung the PCA syringe at a rate of 10cc/hr. Dose should have been 1cc/hr. Patient fortunately suffered no ill effects. This was a sickle cell patient on chronic opiod therapy. This error occurred in a hospital setting. The PCA 3 Abbott PCA pump was used. The custom made Dilaudid syringe was 300 mg/30mL. However, the label also had a line that read (1.00 X a Dose per dose). The nurses interpreted this as 1mg/ml. Error was discovered when PCA pump alarm sounded for empty syringe about 2 hours after being hung. Syringe was added at 2300 and alarm sounded around 0100. PCA pump was programmed wrong and the patient received 300 mg IV Dilaudid over a 2 hour period. This was a sickle cell patient on chronic opiod therapy. Original PCA order was handwritten on a physician order form-preprinted PCA Order Sheet was not utilized. Pharmacy label was confusing in relation to the dilution and in fact the pharmacist mixed this vial with a different concentration than usual. Nurse hung the PCA syringe at a rate of 10cc/br, the dose should have been 1cc/hr.The custom made Dilaudid syringe was 300 mg/30 mL. However, the label also had a line that read (1.00 X 1 Dose per dose). The nurses interpreted this as 1 mg/mL.
5261020	Consumer report from www.abbott.com of aspiration pneumonia, acute lung injury, and overdose coincident with HYDROMORPHONE (DILAUDID) Therapy. On an unreported date, during hospitalization, the patient began DILAUDID therapy for a football injury to the kidneys. On an unknown date, the patient experienced an overdose of DILAUDID therapy, was put on life support, and was in critical condition for six days. On an unreported date, the patient experienced aspiration pneumonia and acute lung injury which prolonged hospitalization. The overdose was considered life-threatening. No further information was available.
5314294	14-Dec-06: A report received from a nurse practitioner, via a sales representative, regarding a female who initiated Actiq (oral transmucosal fentanyl citrate) therapy, 800mcg, for the treatment of

	Fpain related to several back surgeries. The nurse practitioner reported that the patient was taking several other opioid medications including the fentanyl patch and Dilaudid (hydromorphone HCl). On an unknown date, the patient took what "appeared to have been an overdose," and died. No further details were provided. This case has also been forwarded to Abbott and Ortho-McNeill as Dilaudid and fentanyl patch were also considered suspect. 13-Apr-07: Follow-up information received from the nurse practitioner's assistant indicated that according to the toxicology reports, the cause of death was determined to be due to an accidental multiple drug overdose which occurred on an unspecified date in 2006. The patient did not have a history of depression and the patient did not attempt suicide. The patient had been taking Actiq, Duragesic (fentanyl), Valium (diazepam), and other unspecified medications. All medication levels were within therapeutic range. This case has been forwarded to Roche as Valium was also considered suspect; this case has also been sent as follow-up to Abbott and Ortho-McNeill.
5351873	Study phase: Not reported Investigator number: Not reported Study Title: A 12 week Open-Label study with 3 Within-Patient Double Blind Placebo-Controlled Periods to Evaluate the Efficacy and Safety of ORAVESCENT Fentanyl Citrate treatment for the Management of Breakthrough Pain in Opioid-tolerant Patient with Non-cancer Related Chronic Pain Report from the USA of multiple drug overdose, toxic induced encephalopathy, respiratory distress, and pneumonia coincident with DILAUDID in a Cephalon FENTANYL CITRATE study. On (b) (6) the patient's husband reported that the patient was difficult to arouse, and he was unable to obtain a reading on a home blood pressure monitor. He originally called the site and was instructed to call 911. Prior to the arrival of emergency medical technicians, the patient "woke up" and was able to talk. She was transported to the hospital and admitted with altered mental status and respiratory distress. The patient was adminstered NARCAN with significant improvement of her symptoms. A consulting neurologist felt that the patient's symptoms (both neurologic and respiratory) were consistent with a narcotic overdose. Encephalopathy secondary to narcotic use was also diagnosed. In addition, the patient was diagnosed with pneumonia, and received treatment with antibiotics and aerosols. On (b) (6), after an uneventful recovery, the events resolved, and the patient was discharged from the hospital. ALTERNATIVE ETIOLOGY: Event of multiple drug overdose, toxic induced encephalopathy, and respiratory distress Investigator: Not reported Abbott: Events appear to be secondary to narcotic overdose. Event of pneumonia Investigator: Not reported Abbott: Event more likely due to either aspiration or community acquired infection. ********** LABORATORY DATA/COMMENTS: (b) (6) Electroencephalogram: No evidence of acute seizures.
5519003	This was an actual error. RN overrode the Pyxis to remove a Hydromorphone(Dilaudid) 2 mg/mL when in fact she should have removed a Hydromorphone (Dilaudid) 1 mg/mL. Multiple factors lead to this error.

	The 2 mg strength displays first on the Pyxis screen. Both the 1 mg and 2 mg carpujects have brown colored lettering. The 1 mg carpuject is a lighter shade of brown, but they are both brown. This is a hospital setting. The error was caught the following day when the overrides were reviewed. My recommendations are to have Pyxis list the different strengths in numeric order. Also Hospira should have a more Fdramatic color difference between the strengths. Submitted via ISMP Unknown Multiple factors lead to this error. The 2 mg strength displays first on the Pyxis screen. Both the 1 mg and 2 mg carpujects have brown colored lettering. The 1 mg carpuject is a lighter shade of brown, but they are both brown.
5623547	Report reference number GBR-2007-0003565 was received on 18DEC2007 from a physcian via the Regional Centre of Pharmacovigilance and Bristol-Myers Squibb and was reported as below. "A physician reported via BMS France (local file no. 2007-2115) and Agency France (local file no. RN20070208/RN700475) that a 58-year-old female patient experienced coma, diarrhoea, vomiting, acute renal failure and dehydration due to overdose while she was treated with hydromorphone hcl and morphine sulfate for pain and alprazolam for anxiety. The patient received hydromorphone hcl 8 mg twice a day orally for pain, morphine sulphate 20 mg ten times a day orally and alprazolam 0.5 mg three times a day orally. The patient was treated at home for bilateral pneumopathy by amoxicillin + clavuanic acid since 10-Oct-2007. On 16-Oct-2007 the patient experienced coma with pupils in areactive bilateral myosis. She also had diarrhoea and vomiting preventing nutrition since the previous day probably due to amoxicillin + clavulanic acid, acute renal failure with a creatinine of 160 mmol/L (for a usual value of 60) and urea of 17 mmol/L and dehydration. The patient had continued treatment with hydromorphone hcl 8 mg twice a day, morphine sulfate 20 mg as needed (she took up to 10 daily) and alprazolam 0.5 mg three times a day. The patient's outcome was favourable after resuscitation. The patient had a history of many cardiovascular risk factors, chronic respiratory insufficiency, psoriasis with spondylarthropathy treated with adalimumab since Mar-2007, post-corticotherapy secondary iatrogenic adrenal gland insufficiency , obesity, pulmonary embolism, arterial hypertension and non insulin dependent diabetes mellitus. According to the Pharmacovigilance center reporter and to the French methodology of causality assessment, the drug relationship is possible for suspect drugs. BMS Medical Evaluation Comment: This 58-year-old female experienced the reported events while on hydromorphone, morphine sulfate and alprazolam. The concomitant drugs alprazolam, amoxicillin- clavulanic acid and adalimumab can cause diarrhoea and dehydration which could have precipitated acute renal failure. Additional contributory factor was this patient's history of cardiac risk factors, hypertension, obesity and diabetes, any or all of which could have played a causal role in the events of diarrhoea, dehydration and acute renal failure." *** Following internal review on 27DEC2007, the report was updated to include that the trade name for morphine sulfate was Actiskenan. *** Follow up information received on 05FEB2008 from

	the French Regulatory Authority via Abbott (ref: 0833-ALB-07). The report was updated to include additional serious events of bilateral pneumopathy, catheter infection and non-serious event of pupils areactive bilateral miosis. The age of the patient was changed: her date of birth was (b) (6) and she was 57 years old at the time of the first even (b) (6), the patient was admitted in Emergency for bilateral pneumopathy. She declined to be hospitalised. Humira (adalimumab) was discontinued and she was treated with amoxicillin/caluvanic acid at home since 10OCT2007. Bilateral pneumopathy was probably favoured with Humira treatment. On (b) (6) she experienced coma following morphinic and benzodiazepine overdose in a patient with a medical history of acute renal failure (amoxicilline-clavulanic acid induced diarrhoea responsible for dehydration and then hypovolemic shock). Therefore the patient was admitted in Intensive Care Unit and the event improved. Then she Fpresented with sepsis to Multi Resistant Aureus Staphylococcus at catheter level. Therefore the patient was treated with teicoplanine and she recovered. French Drug Agency assessed the causality as probably not related to Humira and considered Humira as not a suspect drug for the coma.
5640736	Our ER Department uses a PYXIS system for dispensing frequently used meds in the ER. The PYXIS machine is filled by Pharmacy Techs. On one day last month the ER physician ordered Hydromorphone 2 mg IV on 2 different patients. What both patients received was Lorazepam 2 mg IV. Our prefilled syringe kits for both Hydromorphone and Lorazepam are both made by Hospira, both contain 2 mg/mL of the drug, and both look nearly identical. The Pharmacy Tech had inadvertently switched the syringes while filling the PYXIS machine and the nurse that administered the drug took the Lorazepam syringes from where the Hydromorphone syringes were supposed to be. She did not notice the medication difference. The Lorazepam 2 mg/mL 1 mL syringes are in a pocket with a hinged lid that opens only when that med is selected for a patient. The Hydromorphone 2 mg/mL 1 mL syringes are located in a separate drawer from the Lorazepam syringes, and are also in a pocket with a hinged lid that only opens when that med is selected for a specific patient. The drawers and pockets for controlled medications are arranged so that the contents of other pockets are not accessible when the drawer is opened -- only the pocket for the selected medication will open when the drawer is opened. Submitted via ISMP There were no major adverse patient events. The medications are pulled in the Pharmacy by a technician from our narcotic storage cabinet, double-checked by a Pharmacist, taken down to the ED in a plastic bucket, and refilled into the ADC by the Pharmacy technician. We do not use bar code technology. The ED ADC is stocked twice daily. Once the medications leave the Pharmacy, the technician is responsible for refilling them into the correct pocket. Even thought the technician had the correct medication when he left the pharmacy, he made an error when restocking the ADC. The nurse

	should verify that the medication being given is the correct medication. It is our hospital's policy that all medications be visually inspected and that the 5 "Rights" of medication administration (including "right drug") be assessed prior to giving a medication. This process must not have occurred in this situation. The expectation that the correct medication is always located in the correct pocket, along with the fact that the two medications are almost identical in appearance, both made by Hospira and both contain 2mg/ml of the drug made conditions favorable for an error to occur. The pharmacy technician who was refilling the ADC was interrupted in the middle of restocking (most likely during the refilling of the Hydromorphone syringes). He logged out so that a nurse could take medication for a patient, and then resumed restocking. Between the time that the refill list was printed and the time that the technician was restocking the machine, the quantity of Lorazepam syringes fell below the par level. When the technician resumed restocking, the Lorazepam pocket opened up to be refilled and he mis-identified the Hydromorphone syringes as Lorazepam syringes. medication error
5689408	A report received from an attorney regarding one hundred forty-one claimants involved in a class action law suit that initiated Actiq (oral transmucosal fentanyl citrate) therapy and allegedly suffered events described as loss of permanent teeth, addiction and overdose requiring medical intervention. 06-Dec-07: Information was received Fin the form of medical records regarding one of the claimants, a 59-year-old Caucasian male, who was receiving Actiq and Duragesic (transdermal fentanyl) for failed back surgery. The patient reported that he was also taking Dilaudid (hydromorphone) 4mg three times daily until Dec-06 and undisclosed amounts of Valium (diazepam). Other relevant medical history includes lumbar spinal stenosis with three back surgeries. On 17-Sep-02, the patient received the first dose of Actiq at a total daily dose of 1200 ug. On (b) (6) approximately four years after the first dose of Actiq, the patient was admitted to the hospital for detoxification treatment of opioid dependence. In addition, In the months prior to hospitalization, the patient was demonstrating erratic behavior indicative of drug dependency and was subsequently released from care by his pain management specialist. Upon admission, Actiq and Duragesic were discontinued and the patient received treatment with Bentyl (dicycloverine hydrochloride), clonidine, quinine, phenobarbital, and low-dose Lyrica (pregabalin). He was induced with Suboxone (buprenorphine HCl/naloxone HCl dihydrate) for withdrawal symptoms. On (b) (6), having done well for several days with no overt withdrawal symptoms noted, the patient was discharged in stable condition. Corporate comment: Dependency is recognized in the product label, and is complicated in this instance by concomitant use of transdermal fentanyl, Valium, Dilaudid, and perhaps alcohol. This case has also been forwarded to Janssen and Abbott as Duragesic and Dilaudid, respectively, were considered secondary suspect medications.

	12-Feb-08: The event of suicidal ideation has been assessed as an Important Medical Event by Cephalon Global Pharmacovigilance and Epidemiology. Follow-up information was received from the attorney in the form of additional medical records. Other relevant medical history included rheumatoid arthritis and depression. Concomitant medication included Xanax (alprazolam),
5699463	A 25-year-old woman who had given birth by Cesarean Section died in the first 24 hours after surgery. She was receiving post-op pain management using an Abbott LifeCare 4100 Plus II pump. It is believed that the dose of hydromorphone the patient received was double the intended amount and the possibility of pump malfunction and/or programming error is being investigated. No further details about cause of death or case specifics are available. Submitted via ISMP.
5829045	Report reference number USA-2008-0034072 was received on 21JUL2008 from a patient's mother via a pharmaceutical company in the United States of America under local case number 07P-163-0360797-00 with additional information received on 23JUL2008 and 29JUL2008 directly from the patient's mother. This spontaneous report refers to a 17-year-old male patient. "Consumer report from www.abbott.com of aspiration pneumonia, acute lung injury, and overdose coincident with HYDROMORPHONE (DILAUDID) Therapy. On an unreported date, during hospitalization, the patient began DILAUDID therapy for a football injury to the kidneys. On an unknown date, the patient experienced an overdose of DILAUDID therapy, was put on life support, and was in critical condition for six days. On an unreported date, the patient experienced aspiration pneumonia and acute lung injury which prolonged hospitalization. The overdose was considered life-threatening. No further information was available." According to the patient's mother, the patient was admitted for a kidney laceration on an unspecified date and was given morphine for pain on (b) (6) (Cross reference to USA-2008-0034073). On 07SEP2006 the patient received his last dose of IV (intravenous) morphine 5 mg at 0343. The patient was still uncomfortable and morphine was switched to [IV] Dilaudid 1 mg which he received at 0648, 0958, 1129, 1231, 1442, and 1603. He also received Toradol (ketorolac) at an unspecified time and dose. The patient was NPO (nothing by mouth) until sometime between 1500 and 1700, when he was given lunch and then became agitated, felt itchy, felt like he had the flu and had a temperature of 103. The nurse gave Phenergan with Dilaudid at an unspecified time. For an unspecified reason, the IV Dilaudid dose was increased to 2 mg, which the patient received at 1712 and 1826, but it was not completely effective in relieving the pain "so the nurse took it upon herself to give him the second dose" at 1943. The patient began to rest and the room lights were turned off. The mother heard the patient snoring, "which he never did", and she called the nurse. When the lights were turned on, the patient was blue. A code was called and during the resuscitation, the patient aspirated vomitus and "developed aspiration pneumonia that led to ARDS" (acute respiratory distress syndrome). The patient received the maximum dose of Narcan (naloxone) and was transferred to the critical care unit. Shortly after transfer, the patient had projectile vomiting and an NG (nasogastric tube) was placed. While in the critical care

	unit, the patient received small doses of morphine IV for pain "if absolutely necessary". The patient was placed on life-support on (b) (6) and was diagnosed with aspiration pneumonia. Discharge had been planned for the next day (b) (6)] but was postponed. Life support was discontinued on (b) (6) and on (b) (6) the patient was diagnosed with an acute lung injury and ARDS. On (b) (6), the patient was discharged with prescriptions for unspecified antibiotics and steroids. According to the reporter "it took some time for him to recover, but he has recovered fully, with no residual impairment". In DEC2006 the patient was "back to normal" and returned to school. The outcome of the events was recovered. The events extra dose administered and aspiration were rated serious due to medical significance, the event overdose was rated serious as it was considered to be life-threatening and intervention required, the event turned blue was rated serious due to intervention required, the event respiratory failure was rated serious due to intervention required and hospitalization prolonged, the events aspiration pneumonia, acute lung injury, and ARDS were rated serious due to hospitalization prolonged. No further information is expected.
5870490	A report received from an attorney regarding one hundred forty-one claimants, involved in a class action lawsuit, who initiated Actiq (oral transmucosal fentanyl citrate) therapy and allegedly suffered events described as loss of permanent teeth, addiction and overdose requiring medical intervention. 02-May-08: Information was received in the form of medical records regarding one of the claimants, a 42-year-old female, who initiated Fentors (fentanyl buccal tablet), 200mcg three times daily as needed, on 27-Oct-06, for the treatment of chronic pain. Secondary suspect medication includes Xanax (alprazolam) 2 mg three times daily, Dilaudid (hydromorphone HCl), Demerol (pethidine HCl), Ambien (zolpidem tartrate) and Actiq (fentanyl citrate). Concomitant medications includes Cymbalta (duloxetine HCl), Zanaflex (tizanidine HCl). Medical history revealed irritable bowel syndrome, chronic migraines, temporomandibular joint syndrome (TMJ) pain, headaches, trigeminal neuralgia, and fibromyalgia. On (b) (6) the consumer was admitted to the hospitalization for inpatient detoxification and stabilization as a result of significant polysubstance abuse, identifying significant opiate and bendodiazepine use. The patient presented with shakiness and tremors as well as nausea, identifying withdrawal distress when she tried to taper or abstain. The consumer also experienced sleep disturbance, as well as panic attacks. She indicated having to cope with chronic pain, resulting in increased opiate use, as well as indicating having been abusing Xanax on a regular basis taking 4 mg four times daily. The consumer was placed on close observation status, and started on Klonopin and Cymbalta and Suboxone protocol to address withdrawal symptoms. The patient experienced continued distress although with a decrease in severity, a decrease in severity of withdrawal symptoms, and improvement in sleep and appetite. On (b) (6), the patient was discharged at to outpatient status. The serious event of polysubstance abuse was assessed as related to Fentora.

	Concurrent use of both Fentora and Actiq therapies is not advised as round the clock maintenance and was therefore considered a medication error. This case has also been forwarded to Pharmacia and Upjohn, Abbott Laboratories, and Sanofi-Aventis as Xanax, Dilaudid, Demerol, Ambien were considered second suspect medications. Corporate comment: Patient was admitted with polysubstance abuse; therefore causal association applies to numerous individual drug compounds.
5922645	A report received from an attorney regarding one hundred forty-one claimants, involved in a class action lawsuit, who initiated Actiq (oral transmucosal fentanyl citrate) therapy and allegedly suffered events described as loss of permanent teeth, addiction and overdose requiring medical intervention. 02-May-08: Information was received in the form of medical records regarding one of the claimants, a 42-year-old female, who initiated Actiq (oral transmucosal fentanyl citrate), 600mcg three times daily as needed, on 07-Jul-04, for the treatment of headaches, trigeminal neuralgia, fibromyalgia and dental pain. Secondary suspect medications included Xanax (alprazolam), 2mg three times daily, Dilaudid (hydromorphone HCl), Demerol (pethidine HCl), Ambien (zolpidem tartrate) and Fentora (fentanyl buccal tablet). Concomitant medications included Cymbalta (duloxetine HCl) and Zanaflex (tizanidine HCl). Medical history revealed facial, neck, lumbar, bilateral knee, and temporomandubular joint pain, as well as irritable bowel syndrome, chronic migraines, and fibromyalgia. On 15-Jun-06, dental views of the patient's mouth indicated severe dental decay. On (b) (6), the she was admitted to the hospital for inpatient detoxification and stabilization as a result of polysubstance abuse, identifying significant opiate and benzodiazepine use. The patient presented with shakiness and tremors, as well as nausea suggesting withdrawal distress when she tried to taper her medications. She also experienced sleep disturbance and panic attacks. The patient complained of having to cope with chronic pain, which resulted in increased opiate use, and she also experienced Xanax abuse on a regular basis, taking 4mg as often as four times a day. She was placed on close observation and started on Klonopin and Cymbalta plus a Suboxone protocol to address withdrawal symptoms. The patient experienced continued distress, although of decreasing severity. She reported a decrease in her withdrawal symptoms and improvement in sleep and appetite. (b) (6), she was discharged to outpatient status. The serious event of polysubstance abuse was assessed as related to Actiq and the non-serious event of severe dental decay was assessed as possibly related to Actiq. Concurrent use of both Actiq and Fentora therapies are not advised as round the clock maintenance and was therefore considered a medication error. See US023505 for associated Fentanyl case.

	This case has also been forwarded to Pharmacia and Upjohn, Abbott Laboratories, and Sanofi-Aventis as Xanax, Dilaudid, Demerol, and Ambien were considered second suspect medications. 25-Jul-08: Further information received in the form of medical records indicated that the patient had sinus surgery in 1997 after which she developed her facial pain. On (b) (6), she had a motor vehicle accident, injuring her neck, low back, left knee, and right shoulder, the residual pain of which had steadily worsened. Her physician noted that many of her complaints were the result of a somatization disorder and psychotherapy was recommended. On-11-Jul-06, she complained that her teeth were "killing her," and she was also having pain from a loose bridge. Available dental records indicated that she had six fillings on 13-Jul-06. 24-Sep-08: Further information received in the form of medical records indicated that, after the onset of facial pain in 1998, she underwent interventional procedures including trigeminal nerve, temporomandibular joint, cervical facet joint, and dorsal trigger point injection as well as pulse wave radiofrequency ablation of the median branch of cervical nerves. The various procedures only provided marginal temporary relief and opioid therapy began on 26-Sep-02 with Ultram (tramadol HCl) and Vicodin (hydrocodone bitartrate, acetaminophen). She was maintained on various opioid analgesics up to her detoxification admission in Mar-07.
6166339	On 3-23-09 at 1200, Good Samaritan Hospital (GSH) (b) (6) notified CAPS Senior Pharmacist (b) (6) that a batch of Hydromorphone (lot#18-2356-0-0 compounded on 2-17-09) was attributed to signs of over-sedation in patients. Two patients were affected. (b) (6) stated that one (1) patient was placed in ICU for monitoring with no harm to the patient. Medication error originated during compounding by Central Admixture Pharmacy Services (CAPS) due to a mathematical error resulting in 1mg/ml strength, not 0.2mg/ml strength as ordered. Two pharmacists and one pharmacy technician were involved in making of the subject lot. Root cause is attributed to human error. Subject drug was compounded in ISO five enviroment. Products inclued in the medication are: Hydromorphone 10mg/ml in 5ml vial manufactured by hospira adn 0.9% Sodium Chloride in 1000ml bag manufactured by BBraun. Central Admixture Pharmacy serviced, Inc, Homewood, Alabama has issued a voluntary product recall of 0.2 mg/ml hydromorphone lot #18-2356-0-0 on April 9th, 2009.
6167909	On 3-23-09 at 1200, Good Samaritan Hospital (GSH) (b) (6)) notified CAPS Senior Pharmacist (b) (6)) that a batch of Hydromorphone (lot#18-2356-0-0 compounded on 2-17-09) was attributed to signs of over-sedation in patients. Two patients were affected. (b) (6) stated that one (1) patient was placed in ICU for monitoring with no harm to the patient. Central Admixture Pharmacy services, Inc. Homewood, Alabama

	has issued a voluntary product recall of 0.2 mg/ml hydromporphone lot #18-2356-0-0 on April 9, 2009. Medication error originated during compounding by Central Admixture Pharmacy Services (CAPS) due to a mathematical error resulting in lmg/ml strength, not 0.2mg/ml strength as ordered. Two pharmacists and one pharmacy technician were involved in making of the subject lot . Root cause is attributed to human error. Subject drug was compounded in ISO five environment. Products included in the medication are: Hydromorphone 10mg/ml in 5ml vial manufactured by hospira and 0.9% Sodium Chloride in 1000ml bag manufacured by BBraun. medication error

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

/s/

ZACHARY A OLESZCZUK
01/13/2011

CAROL A HOLQUIST
01/14/2011