CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200403Orig1s000

CHEMISTRY REVIEW(S)

NDA 200-403

Hydromorphone Hydrochloride Injection

Hospira, Inc.

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-403

2. REVIEW #: 3

3. REVIEW DATE: 26-Oct-2011

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-Apr-2010
Amendment 0001 [a]	25-Jun-2010
Amendment 0002 [a]	27-Aug-2010
Amendment 0003 [b]	20-Sep-2010
Amendment 0004	08-Oct-2010
Amendment 0005 [c]	11-Oct-2010
Amendment 0006 [c]	28-Oct-2010
Amendment 0007	22-Nov-2010
Amendment 0008	23-Nov-2010
Amendment 0009 [a]	30-Apr-2010
Amendment 0010	23-Dec-2010
Amendment 0011 [c]	05-Jan-2011
Amendment 0012	27-Jan-2011

a. Patent Certification information only, not applicable for CMC review.
b. Amended patent certification and exclusivity statement.
c. Responses to microbiological validation information request.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 0015	22-Feb-2011
Amendment 0020	06-Oct-2011
Amendment 0021	10-Oct-2011

Other unlisted amendments up to 10-Oct-2011 are not related to CMC.

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc.
Address:	275 N. Field Dr., Dept. 0389, Bldg. H2-2, Lake Forest, IL 60045
Representative:	Pamela J. Riggio, MS, Regulatory Product Manager
Telephone:	224-212-4636
Fax:	224-212-5401

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hydromorphone HCI Injection, USP
b) Non-Proprietary Name (USAN): Hydromorphone Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 1 mg/mL, 2 mg/mL, and 4 mg/mL

13. ROUTE OF ADMINISTRATION: IV, SC, or IM Injection

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

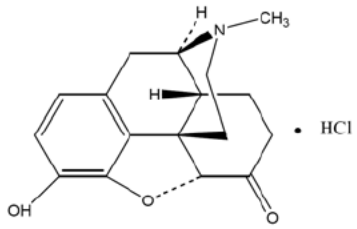
Chemistry Review Data Sheet

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical name: Hydromorphone Hydrochloride
United States Adopted Name (USAN): Hydromorphone Hydrochloride
Compendial name: Hydromorphone Hydrochloride, United States Pharmacopeia (USP)
Chemical structure:



Molecular formula: $C_{17}H_{19}NO_3 \bullet HCl$
Molecular weight: 321.80 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	09-Oct-2007	There has been no change to the DMF that affects its quality since the last review
	III			3	Adequate	16-Aug-2010	There has been no change to the DMF that affects its quality since the last review
	III			7	Adequate	NA	(b) (4)

							(b) (4)

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	17-Sept-2010	Xiaobin Shen
Pharm/Tox	Approval	24-Jan-2011	Dr. Belinda Hayes
Biopharm	Adequate	25-Oct-2010	Dr. Angelica Dorantes
Methods Validation	Not needed	05-Aug-2010	Xiaobin Shen
EA	Adequate	09-Dec-2010	Xiaobin Shen
Microbiology	Approval	25-Jan-2011	Dr. Denise Miller

The Chemistry Review for NDA 200-403

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval. The manufacturing facilities received an overall "Acceptable" cGMP recommendation from the Office of Compliance on May 25, 2010.

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Hydromorphone hydrochloride drug substance is [redacted] (b) (4) Its support is referenced to DMF [redacted] (b) (4) and only limited physicochemical properties are provided in the NDA. The NDA did not provide pharmacological related information about the drug substance, as it is filed in reference to the FDA approved hydromorphone hydrochloride injection Dilaudid®.

The drug substance hydromorphone hydrochloride is manufactured by [redacted] (b) (4) per DMF [redacted] (b) (4) at their [redacted] (b) (4) site. DMF [redacted] (b) (4) was last reviewed by Dr. Sukhamaya Bain in October 2007 to support the approval of ANDA 78-591 and deemed adequate. There has been no change to the DMF that negatively affects its quality since that review.

Specifications for hydromorphone hydrochloride drug substance include both USP requirements and Hospira stipulated test attributes. Collectively they include [redacted] (b) (4) The drug substance is packaged in [redacted] (b) (4). The drug substance stability data was referenced to DMF [redacted] (b) (4) Hospira assigns a retest period of [redacted] (b) (4), and this is supported by stability data in the DMF.

The drug product is a clear, colorless to nearly colorless sterile aqueous solution packaged in USP (b) (4) glass ampules, vials, and cartridges. Its pH range is 3.5 – 5.5. It is intended for intravenous, subcutaneous or intramuscular administration. The strengths include 1 mg/mL, 2 mg/mL, and 4 mg/mL. The excipients include (b) (4) sodium lactate, lactic acid, sodium chloride, (b) (4) and (b) (4) sodium hydroxide. Manufacturing processing (b) (4) Ten product configurations are included in the NDA as summarized in the table below.

Packaging Configuration	Strength (mg/mL)	Fill Volume (mL)	Package Type	Package Capacity (mL)
1	1	1	Ampule	1
2	2	1	Ampule	1
3	4	1	Ampule	1
4	2	1	Vial	2
5	1	1	Carpuject Cartridge	2.5
6	2	1	Carpuject Cartridge	2.5
7	4	1	Carpuject Cartridge	2.5
8	1	1	iSecure Cartridge	1.5
9	2	1	iSecure Cartridge	1.5
10	1	0.5	iSecure Cartridge	1.5

The vials are closed with (b) (4) Gray (b) (4) stoppers and aluminum seals with plastic flip-off tops. The cartridges incorporate 22 gauge Luer Lock needle assemblies, and are sealed with (b) (4) Gray (b) (4) plungers, and capped with aluminum (b) (4) Caps with (b) (4) Gray (b) (4) liners. The (b) (4) Gray (b) (4) materials, was deemed adequate in Dr. Martin Haber's August, 2010 review of DMF (b) (4) The materials meet USP requirements and are suitable for pharmaceutical use. Its specific compatibility to the formulations within this application was demonstrated by absence of leachables from the 18 month real time stability samples.

The hydromorphone hydrochloride injection drug product specifications include appearance, (b) (4) color, identification, volume, assay, pH, related substances, sterility, bacterial endotoxins, and particulate matter. Compliance of container closure integrity was supported by dye immersion testing (b) (4). The drug product stability study was conducted on eight batches, one from each of the packaging configurations tabulated above, except configurations 2 and 6 that were acceptably bracketed, at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). Up to 24 months of long term and 6 month of accelerated stability data have been submitted. (b) (4) total impurities were observed (b) (4)

Despite the observed changes, the provided results conformed to and were well within the proposed acceptance criteria. The provided data is deemed supportive of the claimed 24 months expiry. ICH compliant photostability study was performed using a 2 mg/mL vial product. The study results showed that the drug product is photo labile and a corresponding light protection statement is included on the label.

All IQA comments have been evaluated and resolved.

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

The product is indicated for the management of pain in patients where an opioid analgesic is appropriate.

The proposed treatment regimen is shown below:

- The usual starting dose is 1-2 mg subcutaneously or intramuscularly every [redacted] (b) (4) as necessary for pain control.
- The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydromorphone hydrochloride injection. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use and has shown no detectable leachable by 18 month real time stability samples;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 24 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

XIAOBIN SHEN
11/18/2011
The NDA is recommended for approval from CMC perspective.

PRASAD PERI
11/18/2011
I concur

NDA 200403
Hydromorphone Hydrochloride Injection

(1, 2, and 4 mg/mL)

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

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

Indication: Hydromorphone hydrochloride (schedule II) is indicated for the management of pain in patients where an opioid analgesic is appropriate. The NDA is filed in reference to the FDA approved hydromorphone hydrochloride injection Dilaudid®.

Dosage Regimen The proposed treatment regimen is shown below:
• The usual starting dose is 1-2 mg subcutaneously or intramuscularly every (b) (4) as necessary for pain control.
• The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size.

Presentations: The injections are available in four types of presentations: single use vials 2 mg/mL, single use ampules (1, 2, and 4 mg/mL), Carpuject™ prefilled syringes (1, 2, and 4 mg/mL), and iSecure™ prefilled syringes (1, and 2 mg/mL). See pictures of the presentations at the end of this review.

EER Status: The Office of Compliance has issued an overall acceptable status as of 25-May-2010.

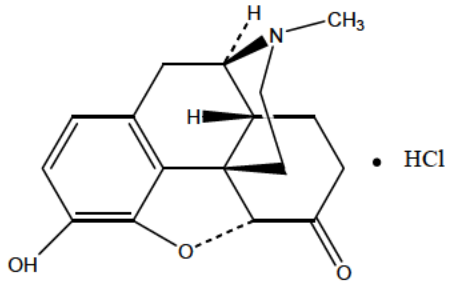
Consults: **EA** – Granted
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology – Acceptable. See PMR for (b) (4)
Biopharmaceutics – Acceptable
Quality Microbiology – Acceptable.

Original Submission: 30-Apr-2010

Post-Approval CMC requirement: The DMF Holder/applicant will be asked to revisit the acceptance criterion (NMT (b) (4) for the specified (b) (4) when its identity is confirmed unambiguously.

Drug Substances: Hydromorphone hydrochloride is (b) (4) It is a hydrogenated ketone of morphine, is an opioid analgesic. The chemical

name of hydromorphone hydrochloride is 4,5α- epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The drug substance hydromorphone hydrochloride is manufactured by (b) (4) per DMF (b) (4) at their (b) (4) site. DMF (b) (4) was reviewed and deemed adequate.



Specifications for hydromorphone hydrochloride drug substance include both USP requirements and Hospira stipulated test attributes. Collectively they include (b) (4) . The DMF holder has a specified impurity ((b) (4) -identity not completely confirmed) specified at a level of (b) (4) which (b) (4) ICH limit of (b) (4) . The DMF holder has other FDA approved products with this (b) (4) . The DMF holder/applicant will be asked to revisit this limit after the identify of this impurity is confirmed and set the appropriate limit in a post approval requirement.

The drug substance is packaged in (b) (4) . The drug substance stability data was referenced to DMF (b) (4) Hospira assigns a retest period of (b) (4) and this is supported by the data.

Conclusion: The drug substance is acceptable.

Drug Product:
The drug product is a clear, colorless to nearly colorless sterile aqueous solution packaged in USP (b) (4) glass ampules, vials, and cartridges. Its pH range is 3.5 – 5.5. It is intended for intravenous, subcutaneous or intramuscular administration. The strengths include 1 mg/mL, 2 mg/mL, and 4 mg/mL. The excipients include (b) (4) sodium lactate, lactic acid, sodium chloride, (b) (4) and (b) (4) sodium hydroxide. Manufacturing (b) (4) Ten product configurations are included in the NDA as summarized in the table below.

The vials are closed with (b) (4) Gray (b) (4) stoppers and aluminum seals with plastic flip-off tops. The cartridges incorporate 22 gauge Luer Lock needle assemblies, and are sealed with (b) (4) Gray (b) (4) plungers, and capped with aluminum (b) (4) Caps with (b) (4) Gray (b) (4) liners. The (b) (4) Gray (b) (4) materials, was deemed adequate during the review of DMF (b) (4) The materials also meet USP requirements and are suitable for pharmaceutical use.

Packaging Configuration	Strength (mg/mL)	Fill Volume (mL)	Package Type	Package Capacity (mL)
1	1	1	Ampule	1
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8	1	1	iSecure Cartridge	1.5
9	2	1	iSecure Cartridge	1.5
10	1	0.5	iSecure Cartridge	1.5

The hydromorphone hydrochloride injection drug product specifications include description, (b) (4) color, identification, volume, assay, pH, related substances, sterility, bacterial endotoxins, and particulate matter. Compliance of container closure integrity was supported by dye immersion testing (b) (4). Sufficient drug product stability studies were conducted on eight batches, one from each of the packaging configuration tabulated on the previous page except configurations 2 and 6 that were acceptably bracketed, at both long term ($25^{o}C/60\%$ RH) and accelerated conditions ($40^{o}C/75\%$ RH) to support the 24 months shelf life for the products. The stability studies also showed that the drug product is photo labile and a corresponding light protection statement is included on the label.

Extractables and leachables studies indicate that the drug product analytical methods do not detect any leachables in the drug product when samples of drug products were tested at the 18 month time point.

The proposed drug product is manufactured, packaged and tested by **Hospira Worldwide Inc. in McPherson, KS**. The manufacturing scale used for the registration batches was (b) (4) or greater of the proposed commercial scale for the various packaging configuration.

Conclusion: The drug product is acceptable.

Outstanding issues: None

Additional Items:

Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

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/s/

PRASAD PERI
01/31/2011

NDA 200-403

Hydromorphone Hydrochloride Injection

Hospira, Inc.

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-403

2. REVIEW #: 2

3. REVIEW DATE: 31-Jan-2011

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
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Amendment 0008 [d]	23-Nov-2010

a. Patent Certification information only, not applicable for CMC review.
b. Amended patent certification and exclusivity statement.
c. Responses to microbiological validation information request.

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Amendment 0011 [c]	05-Jan-2011
Amendment 0012	27-Jan-2011

a. Patent Certification information only, not applicable for CMC review.
c. Responses to microbiological validation information request.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc.
Address:	275 N. Field Dr., Dept. 0389, Bldg. H2-2, Lake Forest, IL 60045
Representative:	Pamela J. Riggio, MS, Regulatory Product Manager
Telephone:	224-212-4636
Fax:	224-212-5401

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hydromorphone HCI Injection, USP
b) Non-Proprietary Name (USAN): Hydromorphone Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesics

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 1 mg/mL, 2 mg/mL, and 4 mg/mL

13. ROUTE OF ADMINISTRATION: IV, SC, or IM Injection

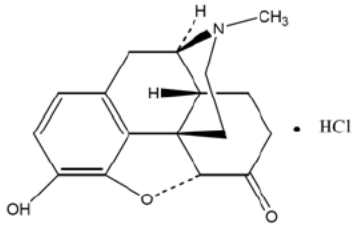
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

__X__Not a SPOTS product

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

Chemical name: Hydromorphone Hydrochloride
United States Adopted Name (USAN): Hydromorphone Hydrochloride
Compendial name: Hydromorphone Hydrochloride, United States Pharmacopeia (USP)
Chemical structure:



Molecular formula: $C_{17}H_{19}NO_3 \bullet HCl$
Molecular weight: 321.80 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	17-Sept-2010	Xiaobin Shen
Pharm/Tox	Approval	24-Jan-2011	Dr. Belinda Hayes
Biopharm	Adequate	25-Oct-2010	Dr. Angelica Dorantes
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Microbiology	Approval	25-Jan-2011	Dr. Denise Miller

The Chemistry Review for NDA 200-403

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A. Recommendation and Conclusion on Approvability

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Hydromorphone hydrochloride drug substance is [redacted] (b) (4) Its support is referenced to DMF [redacted] (b) (4) and only limited physicochemical properties are provided in the NDA. The NDA did not provide pharmacological related information about the drug substance, as it is filed in reference to the FDA approved hydromorphone hydrochloride injection Dilaudid®.

The drug substance hydromorphone hydrochloride is manufactured by [redacted] (b) (4) per DMF [redacted] (b) (4) at their [redacted] (b) (4). DMF [redacted] (b) (4) was last reviewed by Dr. Sukhamaya Bain in October 2007 to support the approval of ANDA 78-591 and deemed adequate. There has been no change to the DMF that affects its quality since that review.

Specifications for hydromorphone hydrochloride drug substance include both USP requirements and Hospira stipulated test attributes. Collectively they include [redacted] (b) (4) The drug substance is packaged in [redacted] (b) (4) The drug substance stability data was referenced to DMF [redacted] (b) (4) Hospira assigns a retest period of [redacted] (b) (4), and this is supported by the DMF.

The drug product is a clear, colorless to nearly colorless sterile aqueous solution packaged in USP (b) (4) glass ampules, vials, and cartridges. Its pH range is 3.5 – 5.5. It is intended for intravenous, subcutaneous or intramuscular administration. The strengths include 1 mg/mL, 2 mg/mL, and 4 mg/mL. The excipients include (b) (4) sodium lactate, lactic acid, sodium chloride, (b) (4) and (b) (4) sodium hydroxide. Manufacturing processing (b) (4) Ten product configurations are included in the NDA as summarized in the table below.

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3	4	1	Ampule	1
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6	2	1	Carpuject Cartridge	2.5
7	4	1	Carpuject Cartridge	2.5
8	1	1	iSecure Cartridge	1.5
9	2	1	iSecure Cartridge	1.5
10	1	0.5	iSecure Cartridge	1.5

The vials are closed with (b) (4) Gray (b) (4) stoppers and aluminum seals with plastic flip-off tops. The cartridges incorporate 22 gauge Luer Lock needle assemblies, and are sealed with (b) (4) Gray (b) (4) plungers, and capped with aluminum (b) (4) Caps with (b) (4) Gray (b) (4) liners. The (b) (4) Gray (b) (4) materials, was deemed adequate in Dr. Martin Haber's Aug, 2010 review of DMF (b) (4) The materials meet USP requirements and are suitable for pharmaceutical use. Its specific compatibility to the formulations within this application was demonstrated by absence of leachables from the 18 month real time stability samples.

The hydromorphone hydrochloride injection drug product specifications include appearance, (b) (4) color, identification, volume, assay, pH, related substances, sterility, bacterial endotoxins, and particulate matter. Compliance of container closure integrity was supported by dye immersion testing (b) (4). The drug product stability study was conducted on eight batches, one from each of the packaging configuration tabulated above except configurations 2 and 6 that were acceptably bracketed, at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). Up to 24 months of testing is planned. 12 months of long term and 6 month of accelerated stability data are submitted. (b) (4) total impurities were observed (b) (4). Despite the observed changes, the provided results conformed to and were well within the proposed acceptance criteria. The provided data is deemed supportive of the claimed 24 months expiry, the extrapolation of expiry from the 12 month real time stability data is based on the trend of the current stability profile. ICH compliant photostability study was performed using a 2 mg/mL vial product. The study

results showed that the drug product is photo labile and a corresponding light protection statement is included on the label.

All IQA comments have been evaluated and resolved.

During the review, information requests were sent to the applicant. Responses to the information request (included in the list of reviewed Amendments) are evaluated at the relevant sections of the Chemistry Review 1. The current review evaluated the remaining responses from the Amendments listed on page 3.

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

The product is indicated for the management of pain in patients where an opioid analgesic is appropriate.

The proposed treatment regimen is shown below:

- The usual starting dose is 1-2 mg subcutaneously or intramuscularly every (b) (4) as necessary for pain control.
- The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydromorphone hydrochloride injection. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use and has shown no detectable leachable by 18 month real time stability samples;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 24 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

XIAOBIN SHEN

01/31/2011

Recommend approval from CMC perspective.
There are comments at end of review to be communicated to the applicant.

PRASAD PERI

01/31/2011

I concur

NDA 200-403

Hydromorphone Hydrochloride Injection

Hospira, Inc.

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-403

2. REVIEW #: 1

3. REVIEW DATE: 19-Jan-2011

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Apr-2010
Amendment 0001 [a]	25-Jun-2010
Amendment 0002 [a]	27-Aug-2010
Amendment 0003 [b]	20-Sep-2010
Amendment 0004	08-Oct-2010
Amendment 0005 [c]	11-Oct-2010
Amendment 0006 [c]	28-Oct-2010
Amendment 0008 [d]	23-Nov-2010

a. Patent Certification information only, not applicable for CMC review.
Other amendments older than the last listed do not have CMC related information for review.
b. Amended patent certification and exclusivity statement.
c. Responses to microbiological validation information request.
d. There is no Amendment 0007 in the eCTD.

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Hospira, Inc.
Address:	275 N. Field Dr., Dept. 0389, Bldg. H2-2, Lake Forest, IL 60045
Representative:	Pamela J. Riggio, MS, Regulatory Product Manager
Telephone:	224-212-4636
Fax:	224-212-5401

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hydromorphone HCl Injection, USP
b) Non-Proprietary Name (USAN): Hydromorphone Hydrochloride
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesics

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 1 mg/mL, 2 mg/mL, and 4 mg/mL

13. ROUTE OF ADMINISTRATION: IV, SC, or IM Injection

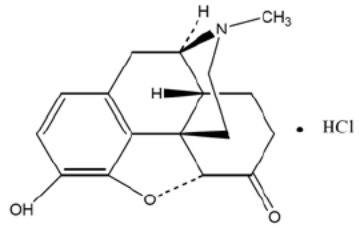
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

__X__Not a SPOTS product

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

Chemical name: Hydromorphone Hydrochloride
United States Adopted Name (USAN): Hydromorphone Hydrochloride
Compendial name: Hydromorphone Hydrochloride, United States Pharmacopeia (USP)
Chemical structure:



Molecular formula: $C_{17}H_{19}NO_3 \bullet HCl$
Molecular weight: 321.80 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	09-Oct-2007	There has been no change to the DMF that affects its quality since the last review
	III			3	Adequate	16-Aug-2010	There has been no change to the DMF that affects its quality since the last review
	III			7	Adequate	NA	(b) (4)

[1] Action codes for DMF Table:

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	17-Sept-2010	Xiaobin Shen
Pharm/Tox	Pending	19-Jan-2011	Dr. Belinda Hayes
Biopharm	Adequate	25-Oct-2010	Dr. Angelica Dorantes
LNC	Pending	19-Jan-2011	NA
Methods Validation	Not needed	05-Aug-2010	Xiaobin Shen
EA	Adequate	09-Dec-2010	Xiaobin Shen
Microbiology	Pending	19-Jan-2011	Dr. Denise Miller

The Chemistry Review for NDA 200-403

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable. The manufacturing facilities received an overall "Acceptable" cGMP recommendation from the Office of Compliance on May 25, 2010.

Leachable assessment is pending. Leachable results from stability samples are to be provided.

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Hydromorphone hydrochloride drug substance is [redacted] (b) (4) Its support is referenced to DMF [redacted] (b) (4) and only limited physicochemical properties are provided in the NDA. The NDA did not provide pharmacological related information about the drug substance, as it is filed in reference to the FDA approved hydromorphone hydrochloride injection Dilaudid®.

The drug substance hydromorphone hydrochloride is manufactured by [redacted] (b) (4) per DMF [redacted] (b) (4) at their [redacted] (b) (4) site. DMF [redacted] (b) (4) was last reviewed by Dr. Sukhamaya Bain in October 2007 to support the approval of ANDA 78-591 and deemed adequate. There has been no change to the DMF that affects its quality since that review.

Specifications for hydromorphone hydrochloride drug substance include both USP requirements and Hospira stipulated test attributes. Collectively they include [redacted] (b) (4) The drug substance is packaged in [redacted] (b) (4). The drug substance stability data was

referenced to DMF (b) (4) Hospira assigns a retest period of (b) (4), and this is supported by the DMF.

The drug product is a clear, colorless to nearly colorless sterile aqueous solution packaged in USP (b) (4) glass ampules, vials, and cartridges. Its pH range is 3.5 – 5.5. It is intended for intravenous, subcutaneous or intramuscular administration. The strengths include 1 mg/mL, 2 mg/mL, and 4 mg/mL. The excipients include (b) (4) sodium lactate, lactic acid, sodium chloride, (b) (4) and (b) (4) sodium hydroxide. Manufacturing processing (b) (4) Ten product configurations are included in the NDA as summarized in the table below.

Packaging Configuration	Strength (mg/mL)	Fill Volume (mL)	Package Type	Package Capacity (mL)
1	1	1	Ampule	1
2	2	1	Ampule	1
3	4	1	Ampule	1
4	2	1	Vial	2
5	1	1	Carpuject Cartridge	2.5
6	2	1	Carpuject Cartridge	2.5
7	4	1	Carpuject Cartridge	2.5
8	1	1	iSecure Cartridge	1.5
9	2	1	iSecure Cartridge	1.5
10	1	0.5	iSecure Cartridge	1.5

The vials are closed with (b) (4) Gray (b) (4) stoppers and aluminum seals with plastic flip-off tops. The cartridges incorporate 22 gauge Luer Lock needle assemblies, and are sealed with (b) (4) Gray (b) (4) plungers, and capped with aluminum (b) (4) Caps with (b) (4) Gray (b) (4) liners. The (b) (4) Gray (b) (4) materials, was deemed adequate in Dr. Martin Haber's Aug, 2010 review of DMF (b) (4) The materials meet USP requirements and are suitable for pharmaceutical use. *Specific compatibility to the formulations within this application will be assessed upon submission of leachable study results by the applicant.*

The hydromorphone hydrochloride injection drug product specifications include appearance, (b) (4) color, identification, volume, assay, pH, related substances, sterility, bacterial endotoxins, and particulate matter. Compliance of container closure integrity was supported by dye immersion testing (b) (4). The drug product stability study was conducted on eight batches, one from each of the packaging configuration tabulated above except configurations 2 and 6 that were acceptably bracketed, at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). Up to 24 months of testing is planned. 12 months of long term and 6 month of accelerated stability data are submitted. (b) (4) total impurities were observed (b) (4). Despite the observed changes, the provided results conformed to and were well within the proposed acceptance criteria. The provided data is deemed supportive of the claimed 24 months expiry, the extrapolation of expiry from the 12

month real time stability data is based on the trend of the current stability profile. ICH compliant photostability study was performed using a 2 mg/mL vial product. The study results showed that the drug product is photo labile and a corresponding light protection statement is included on the label.

All IQA comments have been evaluated and resolved.

During the review, information requests were sent to the applicant. Responses to the information request (included in the list of reviewed Amendments) are evaluated at the relevant sections of this review.

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

The product is indicated for the management of pain in patients where an opioid analgesic is appropriate.

The proposed treatment regimen is shown below:

- The usual starting dose is 1-2 mg subcutaneously or intramuscularly every (b) (4) as necessary for pain control.
- The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydromorphone hydrochloride injection. The product is recommended for approval pending submission of acceptable leachable study results, based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use; *Specific compatibility with this product remains to be demonstrated with leachable study results.*
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 24 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

XIAOBIN SHEN

01/19/2011

The NDA is approvable pending resolution of [redacted] (b) (4) the drug product. There is an information request at end of the review to be communicated to the applicant.

PRASAD PERI

01/19/2011

I concur

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

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	200403	
Chemical Classification	3S	
Applicant:	Hospira	
Stamp date:	April 30, 2010	
PDUFA Date:	February 30, 2010	
Trademark:	NA	
Established Name:	Hydromorphone HCl, USP Injection, USP	
Dosage Form:	Injection, 1 mg/ml; 2 mg/ml; 4 mg/ml	
Route of Administration:	Parenteral (IV, IM SC)	
Indication:	Treatment of acute pain	
CMC Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

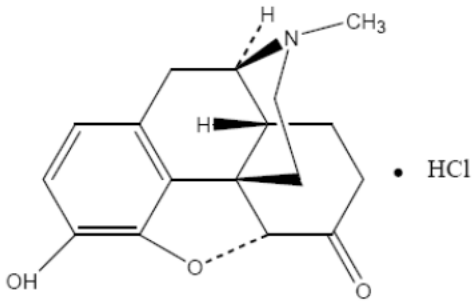
The application is submitted as a 505(b)(2), based on the approved NDA 19-034, Dilaudid® (hydromorphone HCl injection), NDA 19-034, held by Purdue Pharma. This is a marketed unapproved product, by Hospira, and contains lactic acid and sodium lactate, which are not present in the referenced product's formulation. The application is filed based upon the applicant's request for a waiver of *in vivo* bioequivalence or bioavailability studies, as per 21 CFR 320.22. No pre-NDA meeting/agreements have been conducted with the Agency.

The proposed drug product will be available in the same configuration as the referenced product as well as in vials and Carpuject™ and iSecure™ syringes (reference 510k #K063180, iSecure™ Syringe Cartridge Assembly, decision date 12/11/06).

B. Review, Comments and Recommendations

Drug Substance Hydromorphone HCl

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): 4,5 alpha-epoxy-3-hydroxy-17-methyl morphinan-6-one hydrochloride (IUPAC); 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride (CAS)

Molecular formula: $C_{17}H_{19}NO_3$. HCl

Molecular weight: 321.80

CAS: 71-68-1

The drug substance is manufactured by [redacted] (b) (4) and referenced to DMF [redacted] (b) (4) LoA is included in the NDA. [redacted] (b) (4)

Table 1. Impurities in Hydromorphone Hydrochloride

Impurity	Chemical Name	Origin
(b) (4)		

(b) (4)

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Drug product

The drug product is a sterile, non-pyrogenic, [redacted] aqueous solution intended for IV, IM and SC injection. It is available in the following configurations: ampuls of 1 mL capacity; vials of 2 mL capacity, closed with [redacted] gray [redacted] closures and aluminum seals with plastic flip-off tops; cartridges of 2.5 mL capacity (Carpuject) and 1.5 mL capacity iSecure. Both cartridge configurations incorporate 22 gauge Luer Lock needle assemblies, are sealed with [redacted] gray [redacted] elastomeric plungers, and capped with aluminum [redacted] caps with [redacted] gray [redacted] liners. The drug products contain no novel excipients. As discussed, the formulation contains lactic acid and sodium lactate which are not present in Dilaudid® [redacted]

Table 3. Quantitative Composition for Hydromorphone HCl Injection.

Component	Strength		
	1 mg/mL	2 mg/mL	4 mg/mL
	Quantity per unit	Quantity per unit	Quantity per unit
Hydromorphone Hydrochloride USP	1.0 mg	2.0 mg	4.0 mg
Sodium Lactate [redacted] USP	[redacted]		
Sodium Chloride USP, EP, BP			
Lactic Acid USP			
Sodium Hydroxide [redacted]			
q.s. = Quantity sufficient; A.R. = As required			

Note that [redacted].

Pharmaceutical Development:

The applicant stated that the proposed commercial formulation is identical to the historical formulation marketed for 13 years by Hospira. No formulation development, nor significant manufacturing process development have been reported. The osmolality/isotonicity of the drug products has not been discussed, though NaCl has been included as a tonicity agent. The applicant should be questioned with respect to osmolality/isotonicity of the solution, which is a critical physical attribute of the drug product, impacting safety. In addition, the proposed formulations have a different [redacted] than Dilaudid® [redacted]. The applicant stated that [redacted] is a commonly used [redacted] in parenteral drug products. No overages were used.

Manufacturing Process:

The proposed commercial manufacturer is Hospira, McPhearson, Inc., KS. Proposed batch size for the ampuls and vials is [redacted] and for the cartridges up to [redacted] Batch formulae are provided.
The manufacturing process and process controls are described in sufficient detail; flow charts and batch records (master and executed) are included. In-process controls of the [redacted] solution(s), are: [redacted] The manufacturing process consists of

(b) (4). The applicant requires container closure intergrity validation for vials, Carpuject and iSecure. The manufacturing process and finished products are kept (b) (4). Hold times of the (b) (4) solutions are based on validation data of the lowest strength and set at (b) (4) (report PQR0056.00-06-02). This should be assessed upon review, as morphine and its derivatives are photosensitive and susceptible to oxidation.

Process validation:
Process validation studies have been performed for the (b) (4) Results for hold times are reported for batches 39800LL, 39790LL and 39795LL (lowest strength). Process validation studies and adequacy of the (b) (4) process should be assessed in consultation with the Microbiology Division.

Extractables/leachables evaluation:
The applicant performed USP 28 <381> testing on the (b) (4) closures for injections and extractables in (b) (4), concluding that no appreciable differences have been observed between blank and test samples. No leachables have been monitored in the drug product. The adequacy of this study should be assessed upon review.

Compatibility with infusion solutions and diluents:
Compatibility of a 0.08 mg/ml concentration has been tested at t = 0 and 24h with the following diluents:
0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
5% Dextrose / 0.9% Sodium Chloride Injection, USP
5% Dextrose in Lactated Ringers, USP
Sodium Lactate Injection (1/6 M), USP
Attributes tested were appearance, pH change, hydromorphone assay, degradants and particulate matter as per USP SVP limits. The applicant concluded that the solution was stable with the above diluents in (b) (4) containers for IV infusion.

Drug Product Specifications:

The proposed specifications are based on the USP monograph; the Hospira limit of bacterial endotoxin (b) (4) than the USP. Two degradants are controlled, (b) (4) at NMT (b) (4). Since this was (b) (4) product, monitoring of additional potential degradants with possible structural alerts should be assessed after review of the drug substance stability data in the DMF.
Impurities/degradants' specifications should be assessed as per ICHQ3B(R) and the draft FDA Guidance on structural alerts, in consultation with the Toxicology Division. The pH range of 3.5 – 5.5 should be compared with the pH during manufacture and evaluated upon review. Methods validation for the non-compendial methods is provided and should be assessed as per ICH Q2B.

Table 3. Proposed Specifications for Hydromorphone HCl Injection

Standard Claimed	USP		
Specification Reference Numbers	H-0340, H-0341, H-0342, H-0540, H-0541, H-0542, H-0543		
USP Test	**Acceptance Criteria**	**Regulatory Analytical Procedure**	**Alternate Analytical Procedure**
Identification (IR)	Conforms to reference standard	USP IR	
pH <791>	3.5 - 5.5	USP <791>	
Volume <1>	NLT labeled volume	USP <1>	
Hydromorphone HCl	(b) (4) mg/mL [1 mg/mL product] mg/mL [2 mg/mL product] mg/mL [4 mg/mL product]	USP UV	In-house HPLC, AP # PR-1370 [a,b,c]
Hydromorphone HCl Label Claim	(b) (4) of label claim	USP UV	In-house HPLC, AP # PR-1370 [a,b,c]
Sterility <71>	Meets USP requirements	USP <71> [d]	
Bacterial Endotoxins <85>	NMT (b) (4) EU/mg Hydromorphone HCl[f]	USP <85> [d]	
Particulate Matter <788>	NMT (b) (4) NMT	USP <788>	
(b) (4)			
Additional Hospira Testing	**Acceptance Criteria**	**Procedure**	
Description (Appearance)	Clear, colorless to nearly colorless solution	Visual	
Identification (HPLC)	Same retention time as reference standard	In-house HPLC, AP # PR-1370 [a,b]	
Degradation Products/ Related Impurities: (b) (4)	NMT (b) (4) NMT NMT NMT	In-house HPLC, AP # PR-1370 [a,b]	
(b) (4) Color	NMT	In-house, AP # PR-0451 [a]	

Batch analysis data:

Eight batches submitted in the NDA:

Ampuls: 76590DD 1 mg/ml, 76595DD, 4 mg/ml; 1ml fill in 1 ml ampule

Vials: 76605DD 2 mg/ml; 1 ml fill in 2 ml vial

Carpuject®: 77600LL 1 mg/ml, 77795LL, 4 mg/ml 1 ml fill in 2.5 ml cartridge

iSecure®: 76590DD 2 mg/ml, 1 ml fill in a 1.5 ml cartridge; 76595DD, 1 mg/ml, 0.5 ml fill in a 1.5 ml cartridge.

Scale: (b) (4). Batch analysis data met specifications; (b) (4).

Note that the applicant indicated that these are "representative batches" and bracketed the 2mg/ml strength for the ampul and Carpuject® (cartridge) configurations. The submitted data should be assessed for adequacy to cover all proposed fills/configurations; additional supporting data may be requested upon review.

Container Closure System:
The container/closure system has been discussed on p. 1 and 5. Note that the cartridges/syringe assemblies are not "autoinjectors" but manual. In addition, these are new packaging configurations for the current product, not included in the Dilaudid® label. A reference has been provided for the regulatory status of iSecure® (510k clearance) and this should be confirmed upon review. Summary of the components, suppliers and DMF references are included in the NDA. Suitability of the container/closure system should be assessed (Section 3.2.P.2).

Stability:
Stability testing of the drug products is performed at long-term (25°C/60% RH), and accelerated (40°C/75 % RH) storage conditions. The firm submitted 9-month long term data and 6-month accelerated stability data on the eight NDA batches and requested a 24-month expiry. The 2mg/ml strength was bracketed in the ampul and Carpuject (cartridge) configurations. However, no information was submitted with respect to testing in inverted configurations (vials and cartridges). The applicant stated that historical data support the requested expiry and that the formulation/configuration(s) have not changed; therefore, additional data may be requested from the applicant. In addition, the applicant stated that the drug product is protected from light by the secondary packaging. Photostability data have not been submitted. Sterility is to be retested at (b) (4), and bacterial endotoxin at (b) (4). The submitted data show no significant degradation up to 9-months; all monitored impurities remain (b) (4)

Labeling
Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling has not been included in M1.

C. Critical issues for review and recommendation

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

1. The [redacted] DMF [redacted] should be assessed. The applicant should be questioned with respect to the chemical structures of impurities identified as [redacted] which do not correspond to the Ph. Eur. impurities [redacted]
Impurities should be assessed for structural alerts and the suitability of the proposed drug [redacted] specifications should be assessed as per ICH Q3A(R) and the draft FDA Guidance on structural alerts in consultation with the Toxicology Division. Suitability of the analytical method, (Hospira HPLC AP#PR-1471) and its validation including LOD/LOQs should be assessed as per ICHQ2b(R).
2. Suitability of the drug product manufacturing process, which includes [redacted] should be assessed in consultation with the Microbiology division. In addition, in-process controls, microbiolgical integrity of the closures, and process validation should be assessed.
3. Hold times [redacted] in the finished product, should be assessed.
4. The drug product contains NaCl as a tonicity agent. Osmolality/isotonicity of the drug product should be assessed.
5. The specification for the end-product pH range of 3.5 – 5.5 should be compared with the target pH during manufacture and evaluated upon review. Note that a different [redacted] is used in the current product [redacted] instead of the approved product Dilaudid® [redacted]
6. Compatibility of the drug product with common diluents and drugs used for IV infusion.
7. Specifications for drug product impurities/degradants as per ICHQ3B(R) in consultation with the Toxicology Division.
8. Adequacy of the information provided for extractables, suitability and compatibility of the packaging system, including the leachables/extractables evaluation should be assessed in consultation with the Toxicology division.
9. Regulatory status of the iSyringe® cartridge system.
10. Proposed expiration dating of 24 months, including storage orientations, conditions of storage and adequacy of the NDA batches as representative data for all proposed commercial configurations.
11. Photostability data as per ICH Q1B have not been included and should be requested. The drug product is claimed to be protected from light by the secondary packaging.
12. Labeling in SPL format.

D. Comment for the 74-day Letter:

1. Provide an updated summary for the primary stability batches included in the NDA. In addition, provide stability data in inverted configurations, e.g., vials, Carpuject® and iSyringe® cartridges.
2. Provide photostability data for the drug product, as per ICH Q1B.
3. You have provided extractables assessment for the [redacted] closures for injections and no information on leachables assessment in all of the proposed drug product packaging configurations. Provide adequate justification (including supportive data) for the absence of leachables in all of your proposed packaging configurations.

4. Provide the structure and CAS numbers for the drug substance impurities (b) (4) [redacted]

E. **Recommendation for fileability**: The NDA is fileable based on sufficient number of primary stability batches, and 9- month real time stability data at 25°C/40% RH based on a biowaiver request to the approved product Dilaudid®. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

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

Consults:

1. Microbiology (requested; assigned reviewer: Denise Miller)
2. Biopharmaceutics, ONDQA (requested; reviewer: Angelica Dorantes)
3. Toxicology (to be determined and initiated by the primary reviewer)

Danae D Christodoulou, Ph.D. — 6/29/2010
CMC Lead — Date

Prasad Peri, Ph.D. — 7/1/2010
Acting Branch VIII Chief, ONDQA — Date

NDA Number: 200403 **Supplement Number and Type: 3S** **Established/Proper Name: Hydromorphone HCl injection**

Applicant: Hospira **Letter Date: 04/30/2010** **Stamp Date: 4/30/2010**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

{See appended electronic signature page}

Name of
PAL: Danae Christodoulou 6/29/10 Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief (Acting): Prasad Peri Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

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

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

/s/

DANAE D CHRISTODOULOU
07/01/2010
Initial Quality Assessment

PRASAD PERI
07/01/2010