CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022234Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-234

Amendment

Docetaxel Injection

Hospira Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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Chemistry Review Data Sheet

1. NDA 22-234 Amendment

2. REVIEW #5

3. REVIEW DATE: 02-FEB-2011

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	11-JUL-2007
Amendment (BC)	14-MAR-2008
Amendment (BL)	24-APR-2008
Amendment (BC)	08-MAY-2008
Review #1	08-JUL-2008
Amendment (BL) – Revised carton and content of labeling	30-JUL-2008
Amendment (BL) – Revised Carton and Container Labels	08-AUG-2008
Amendment (BL) – Updated Labeling	11-AUG-2008
Amendment (RD) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment (BZ) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment – Response to Chemistry Deficiencies Review # 2	03-DEC-2009
Amendment – Request for Withdrawal Labeling	11-DEC-2009
Amendment – General Correspondence – Clarification re: Tentative Approval	11-MAR-2010
Minor Amendment – Full Approval Request; based on 11-AUG-2008 and 11-DEC-2009 Tentative Approval Letters.	23-SEP-2010
(b) (4) (b) (4)	03-NOV-2010
Telephone Request - Labeling	08-NOV-2010
Telephone Request – Recent Revision of Labeling	09-NOV-2010
Telephone Request – Key Diff. between Hospira vs Sanofi Formula	11-NOV-2010
Patent Information Amendment	15-NOV-2010
Labeling (Carton and Container) Labeling	23-NOV-2010
Labeling (Carton and Container) Labeling	24-DEC-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Labeling Amendment	27-JAN-2011

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira Inc.
Address:	275 North Field Dr Dept. 389, Bldg. H2-2 Lake Forest, IL 60045
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg/2 mL, 80 mg/8 mL, 160 mg/16 mL

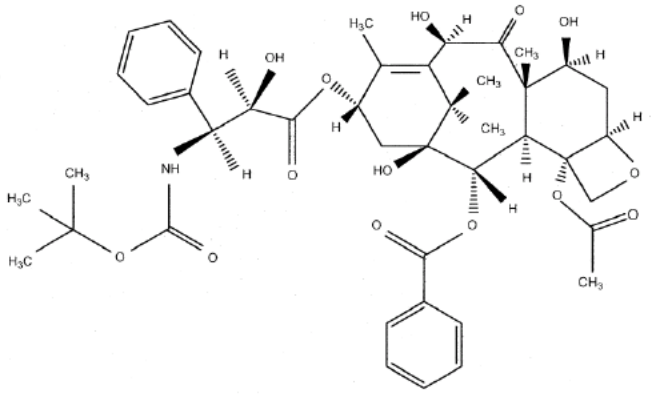
13. ROUTE OF ADMINISTRATION: Injection

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:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



Empirical formula: $C_{43}H_{53}NO_{14}$ Molecular weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008	By T. Ocheltree
	III			3	Adequate	03-OCT-2007	By J. Chang
	III			3	Adequate	08-JUL-2008	By T. Ocheltree
	V			3	Adequate	03-AUG-2009	By Rona LeBlanc

[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
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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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
None					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		Acceptable	09-DEC-2009
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	09/JUN-2008	Approve as 505(b)(2) / M. Brower	Acceptable
Biopharm	N/A			
ODS/DMEPA	Labeling consult	04-AUG-2008, 14-DEC-2010, 28-JAN-2011	Loretta Holmes	Acceptable
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	(b) (4)	06-JUN-2008 24-NOV-2009	Approval (1st cycle) Approval (2nd Cycle)	Dr. A. Lolas (first review cycle) 2nd. Cycle reviewed by B. Riley, Ph.D. 10-DEC-2009

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is approval with respect to chemistry, manufacturing, and controls (CMC).
The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see Microbiology Review). Hospira has addressed the CMC comments related to carton and container labels in Amendment dated 27-Jan-2011; see attached copies of revised carton and container labels.

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

None

II. Summary of Chemistry Assessment – See Chemistry Review #1

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product
Docetaxel injection is formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. Taxotere preparation requires a two-step dilution prior to IV administration, where as the proposed product is added directly to the IV solution. The proposed undiluted docetaxel injection formulation contains the same drug substance (b) (4) as diluted Taxotere (following the initial dilution). The proposed drug product also contains polyethylene glycol 300 (b) (4) and citric acid (b) (4). It will be marketed as a 10 mg/mL formulation in three packaging configurations (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL) in contrast to the reference listed drug (RLD). The RLD contains 20 or 80 mg of drug formulated in 0.5 ml or 2 ml of polysorbate 80. Additionally, the 80 mg/8 mL, and 160 mg/16 mL presentations are multi-use vials, which is not available for the RLD. All three presentations consist of Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals. The container closure system for the ZHOPL manufacturing site is the same as the original with exception of the (b) (4) stoppers.
According to the applicant these presentation were developed based on considerations of patient dose, practitioner convenience, less risk of exposure to toxic compounds, reduced potential for contamination, and less hazardous waste being formed.

The proposed drug product is manufactured by [redacted] The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A [redacted] expiry date is proposed based on 12 months of long term and 6 months accelerated stability data. While a [redacted] expiry was granted in the first review (see Chemistry Review #1), a [redacted] (18-month) expiry is granted for amendment dated 12-JUN-2009, due to a decreased amount of data for the proposed site, Zydus, India.

[redacted] The maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B) and were consulted to the Pharmacology/Toxicology reviewer for assessment. The Pharmacology/Toxicology reviewer confirmed that these levels were adequate. This information applies to both facility sites, Mulgrave, Australia and Zydus, India.

Drug Substance

Docetaxel is an anhydrous, white to off-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may influence drug product performance and manufacturability. A major [redacted] impurity [redacted] is formed by [redacted]. X-ray diffraction has identified [redacted] morphic forms [redacted] It is reported that the desired morphic form [redacted] is produced during manufacture [redacted].

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in [redacted] bags, in [redacted] bottle with desiccants placed between the bags and bottle.

The manufacturing process is referenced to DMF [redacted].

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m2. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, [redacted]

C. Basis for Approvability or Not-Approval Recommendation

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-

DEC-2009 (see Microbiology Review). However, there are some issues with the carton and container labeling to correct; see IA.

III. Administrative

This NDA Amendment was submitted in electronic format as a 505(b)(2) application. A Quality Overall Summary is included in the original application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

J.Jee/ONDQA/Reviewer
S.Pope /ONDQA/Branch Chief
R. Lostritto/ONDQA/Div. I/Director

C. CC Block

D.Mesmer/ONDQA/Regulatory PM
F.Cross/DDOP/Regulatory PM
H.Sarker/ONDQA/CMC Lead

26 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

JOSEPHINE M JEE
02/04/2011

HARIPADA SARKER
02/07/2011

SARAH P MIKSINSKI
02/08/2011

NDA 22-234

Amendment

Docetaxel Injection

Hospira Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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S DRUG SUBSTANCE [Docetaxel, (b) (4)] 11

S.1 General Information 11
S.2 Manufacture 11
S.3 Characterization ..... **Error! Bookmark not defined.**
S.4 Control of Drug Substance ..... **Error! Bookmark not defined.**
S.5 Reference Standards or Materials ..... **Error! Bookmark not defined.**
S.6 Container Closure System ..... **Error! Bookmark not defined.**
S.7 Stability ..... **Error! Bookmark not defined.**

P DRUG PRODUCT [Docetaxel Injection, Hospira] ..... **Error! Bookmark not defined.**

P.1 Description and Composition of the Drug Product ..... **Error! Bookmark not defined.**
P.2 Pharmaceutical Development 22
P.3 Manufacture 22
P.4 Control of Excipients 22
P.5 Control of Drug Product 22
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Chemistry Review Data Sheet

1. NDA 22-234 Amendment

2. REVIEW #4

3. REVIEW DATE: 14-JAN-2011/ 21-JAN-2011

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	11-JUL-2007
Amendment (BC)	14-MAR-2008
Amendment (BL)	24-APR-2008
Amendment (BC)	08-MAY-2008
Review #1	08-JUL-2008
Amendment (BL) – Revised carton and content of labeling	30-JUL-2008
Amendment (BL) – Revised Carton and Container Labels	08-AUG-2008
Amendment (BL) – Updated Labeling	11-AUG-2008
Amendment (RD) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment (BZ) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment – Response to Chemistry Deficiencies Review # 2	03-DEC-2009
Amendment – Request for Withdrawal Labeling	11-DEC-2009
Amendment – General Correspondence – Clarification re: Tentative Approval	11-MAR-2010
Minor Amendment – Full Approval Request; based on 11-AUG-2008 and 11-DEC-2009 Tentative Approval Letters.	23-SEP-2010
(b) (4) (b) (4)	03-NOV-2010
Telephone Request - Labeling	08-NOV-2010
Telephone Request – Recent Revision of Labeling	09-NOV-2010
Telephone Request – Key Diff. between Hospira vs Sanofi Formula	11-NOV-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Patent Information Amendment	15-NOV-2010
Labeling (Carton and Container) Labeling	23-NOV-2010
Labeling (Carton and Container) Labeling	24-DEC-2010

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira Inc.
Address:	275 North Field Dr Dept. 389, Bldg. H2-2 Lake Forest, IL 60045
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg/2 mL, 80 mg/8 mL, 160 mg/16 mL

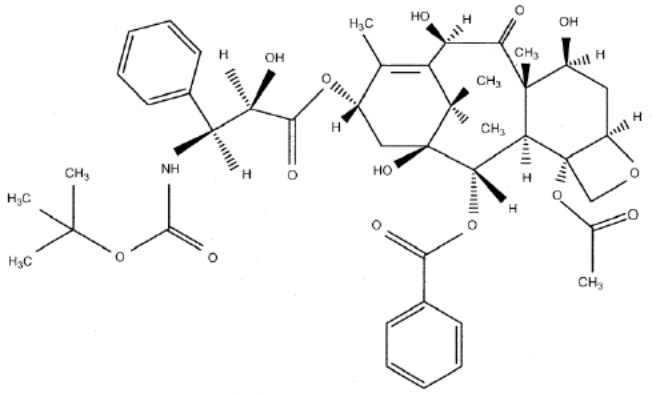
13. ROUTE OF ADMINISTRATION: Injection

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:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



Empirical formula: $C_{43}H_{53}NO_{14}$ Molecular weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008	By T. Ocheltree
	III			3	Adequate	03-OCT-2007	By J. Chang
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	V			3	Adequate	03-AUG-2009	By Rona LeBlanc

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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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)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
None					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		Acceptable	09-DEC-2009
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	09/JUN-2008	Approve as 505(b)(2) / M. Brower	Dr. M. Brower
Biopharm	N/A			
ODS/DMEPA	Labeling consult	04-AUG-2008 and -NOV-2010	Loretta Holmes	Review with comments
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	(b) (4)	06-JUN-2008 24-NOV-2009	Approval (1st cycle) Approval (2nd Cycle)	Dr. A. Lolas (first review cycle) 2nd. Cycle reviewed by B. Riley, Ph.D. 10-DEC-2009

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is approval with respect to chemistry, manufacturing, and controls (CMC).
The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see Microbiology Review). However, Hospira should address the comments related to carton and container labels; see below.

1. Utilize one uniform set of carton and container labels for drug products manufactured by either Hospira Australia Pty Ltd, Mulgrave, Australia or by Zydus Hospira Oncology Private Ltd., Gujara, India. The only site-specific difference in these labels should be the different manufacturing sites and their addresses.

2. Replace [redacted] (b) (4) with "Manufactured by: Hospira Australia Pty Ltd., Mulgrave, Australia. Distributed by: Hospira Inc., Lake Forest, IL 60045, USA" and [redacted] (b) (4) with "Manufactured by: Zydus Hospira Oncology Private Ltd., Gujara, India. Distributed by: Hospira Inc., Lake Forest, IL 60054, USA". Apply this revision to all carton and container labels.

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

None

II. Summary of Chemistry Assessment – See Chemistry Review #1

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product
Docetaxel injection is formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. Taxotere preparation requires a two-step dilution prior to IV administration, where as the proposed product is added directly to the IV solution. The proposed undiluted docetaxel injection formulation contains the same drug substance [redacted] (b) (4) as diluted Taxotere (following the initial dilution). The proposed drug product also contains polyethylene glycol 300 [redacted] (b) (4) and citric acid [redacted] (b) (4). It will be marketed as a 10 mg/mL formulation in three packaging configurations (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL) in contrast to the reference listed drug (RLD). The RLD

contains 20 or 80 mg of drug formulated in 0.5 ml or 2 ml of polysorbate 80. Additionally, the 80 mg/8 mL, and 160 mg/16 mL presentations are multi-use vials, which is not available for the RLD. All three presentations consist of Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals. The container closure system for the ZHOPL manufacturing site is the same as the original with exception of the (b) (4) stoppers. According to the applicant these presentation were developed based on considerations of patient dose, practitioner convenience, less risk of exposure to toxic compounds, reduced potential for contamination, and less hazardous waste being formed.

The proposed drug product is manufactured by (b) (4) The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A (b) (4) expiry date is proposed based on 12 months of long term and 6 months accelerated stability data. While a (b) (4) expiry was granted in the first review (see Chemistry Review #1), a (b) (4) (18-month) expiry is granted for amendment dated 12-JUN-2009, due to a decreased amount of data for the proposed site, Zydus, India.

(b) (4) The maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B) and were consulted to the Pharmacology/Toxicology reviewer for assessment. This information applies to both facility sites, Mulgrave, Australia and Zydus, India.

Drug Substance

Docetaxel is an anhydrous, white to off-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may influence drug product performance and manufacturability. A major (b) (4) impurity (b) (4) is formed by (b) (4). X-ray diffraction has identified (b) (4) morphic forms (b) (4) It is reported that the desired morphic form (b) (4) is produced during manufacture (b) (4).

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in (b) (4) bags, in (b) (4) bottle with desiccants placed between the bags and bottle.

The manufacturing process is referenced to DMF (b) (4).

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m2. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, (b) (4)

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see Microbiology Review). However, there are some issues with the carton and container labeling to correct; see IA.

III. Administrative

This NDA Amendment was submitted in electronic format as a 505(b)(2) application. A Quality Overall Summary is included in the original application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

J.Jee/ONDQA/Reviewer
S.Pope /ONDQA/Branch Chief
R. Lostritto/ONDQA/Div. I/Director

C. CC Block

D.Mesmer/ONDQA/Regulatory PM
F.Cross/DDOP/Regulatory PM
H.Sarker/ONDQA/CMC Lead

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/s/

JOSEPHINE M JEE
01/24/2011

HARIPADA SARKER
01/25/2011

SARAH P MIKSINSKI
02/01/2011

NDA 22-234

Amendment

Docetaxel Injection

Hospira Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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II. Summary of Chemistry Assessment 9

A. Description of the Drug Product(s) and Drug Substance(s) 9

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C. CC Block 10

Chemistry Assessment **11**

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S DRUG SUBSTANCE [Docetaxel, (b) (4)] 11

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S.4 Control of Drug Substance 13
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P.2 Pharmaceutical Development 22
P.3 Manufacture 22
P.4 Control of Excipients 22
P.5 Control of Drug Product 22
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P.7 Container Closure System 22

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Chemistry Review Data Sheet

1. NDA 22-234 Amendment

2. REVIEW #3

3. REVIEW DATE: 12-NOV-2010

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	11-JUL-2007
Amendment (BC)	14-MAR-2008
Amendment (BL)	24-APR-2008
Amendment (BC)	08-MAY-2008
Review #1	08-JUL-2008
Amendment (BL) – Revised carton and content of labeling	30-JUL-2008
Amendment (BL) – Revised Carton and Container Labels	08-AUG-2008
Amendment (BL) – Updated Labeling	11-AUG-2008
Amendment (RD) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment (BZ) – Add Alternate Man. Site for DP Review # 2	12-JUN-2009
Amendment – Response to Chemistry Deficiencies Review # 2	03-DEC-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment – Request for Withdrawal Labeling Amendment	11-DEC-2009
Amendment – General Correspondence – Clarification re: Tentative Approval	11-MAR-2010
Minor Amendment – Full Approval Request; based on 11-AUG-2008 and 11-DEC-2009 Tentative Approval Letters. (b) (4) .	23-SEP-2010
(b) (4)	03-NOV-2010
Telephone Request - Labeling	08-NOV-2010
Telephone Request – Recent Revision of Labeling	09-NOV-2010
Telephone Request – Key Diff. between Hospira vs Sanofi Formula	11-NOV-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Hospira Inc.

Executive Summary Section

Address:	275 North Field Dr Dept. 389, Bldg. H2-2 Lake Forest, IL 60045
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg/2 mL, 80 mg/8 mL, 160 mg/16 mL

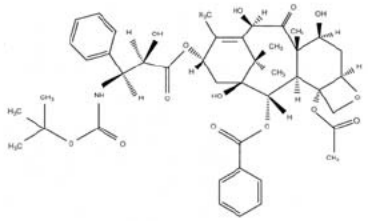
13. ROUTE OF ADMINISTRATION: Injection

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:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



The empirical formula: $C_{43}H_{53}NO_{14}$ The molecular weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008	By T. Ocheltree
	III			3	Adequate	03-OCT-2007	By J. Chang
	III			3	Adequate	08-JUL-2008	By T. Ocheltree
	V			3	Adequate	03-AUG-2009	By Rona LeBlanc

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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
None					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
None			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		Acceptable	09-DEC-2009
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	09/JUN-2008	Approve as 505(b)(2) / M. Brower	Dr. M. Brower
Biopharm	N/A			

Executive Summary Section

ODS/DMEPA	Labeling consult	04-AUG-2008 and -NOV-2010	Loretta Holmes	Review with comments
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	(b) (4)	06-JUN-2008 24-NOV-2009	Approval (1st cycle) Approval (2nd Cycle)	Dr. A. Lolas (first review cycle) 2nd. Cycle reviewed by B. Riley, Ph.D. 10-DEC-2009

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is approval with respect to chemistry, manufacturing, and controls (CMC).
The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see Microbiology Review). However, Hospira should address the comments related to carton and container labels; see below.

1. Carton Labels:
   A. The expiration date and Lot number must be included in the vial labels of 2 mL, 8 mL , and 16 mL vial manufactured in Australia.
   B. List excipients in either of the 2ml vial labels from Australia and from India.
   C. Replace storage condition by (b) (4)
   D. Replace "For IV Infusion Only" by Intravenous Use Only
   E. Replace Sterile by Sterile Solution
   F. Increase the prominence of Rx
   G. Replace (b) (4) by Manufactured by: Hospira Australia Pty Ltd., Mulgrave, Australia. Distributed by: Hospira Inc., Lake Forest, IL 60045, USA
   H. Replace (b) (4) by Manufactured by: Zydus Hospira Oncology Private Ltd., Gujara, India. Distributed by: Hospira Inc., Lake Forest, IL 60054, USA.

2. Container Labels:
   A. The expiration date and Lot number must be included in the vial labels of 2 mL, 8 mL , and 16 mL vial manufactured in Australia.
   B. List excipients in either of the 2ml vial labels from Australia and from India.
   C. Replace storage condition by (b) (4)
   D. Replace "For IV Infusion Only" by Intravenous Use Only
   E. Replace Sterile by Sterile Solution
   F. Increase the prominence of Rx
   G. Replace (b) (4) by Manufactured by: Hospira Australia Pty Ltd., Mulgrave, Australia. Distributed by: Hospira Inc., Lake Forest, IL 60045, USA
   H. Replace (b) (4) by Manufactured by: Zydus Hospira Oncology Private Ltd., Gujara, India. Distributed by: Hospira Inc., Lake Forest, IL 60054, USA.

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

None

II. Summary of Chemistry Assessment – See Chemistry Review #1

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Docetaxel injection is formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. Taxotere preparation requires a two-step dilution prior to IV administration, where as the proposed product is added directly to the IV solution. The proposed undiluted docetaxel injection formulation contains the same drug substance (b) (4) as diluted Taxotere (following the initial dilution). The proposed drug product also contains polyethylene glycol 300 (b) (4) and citric acid (b) (4). It will be marketed as a 10 mg/mL formulation in three packaging configurations (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL) in contrast to the reference listed drug (RLD). The RLD contains 20 or 80 mg of drug formulated in 0.5 ml or 2 ml of polysorbate 80. Additionally, the 80 mg/8 mL, and 160 mg/16 mL presentations are multi-use vials, which is not available for the RLD. All three presentations consist of Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals. The container closure system for the ZHOPL manufacturing site is the same as the original with exception of the (b) (4) stoppers. According to the applicant these presentation were developed based on considerations of patient dose, practitioner convenience, less risk of exposure to toxic compounds, reduced potential for contamination, and less hazardous waste being formed.

The proposed drug product is manufactured by (b) (4) The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A (b) (4) expiry date is proposed based on 12 months of long term and 6 months accelerated stability data. While a (b) (4) expiry was granted in the first review (see Chemistry Review #1), a (b) (4) (18-month) expiry is granted for amendment dated 12-JUN-2009, due to a decreased amount of data for the proposed site, Zydus, India.

(b) (4) The maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B) and were consulted to the Pharmacology/Toxicology reviewer for assessment. This information applies to both facility sites, Mulgrave, Australia and Zydus, India.

Drug Substance

Docetaxel is an anhydrous, white to off-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may influence drug product performance and manufacturability. A major (b) (4) impurity (b) (4) is formed by (b) (4). X-ray diffraction has identified (b) (4) morphic forms (b) (4)

[redacted] (b) (4) It is reported that the desired morphic form [redacted] (b) (4) is produced during manufacture via [redacted] (b) (4).

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in [redacted] (b) (4) bags, in [redacted] (b) (4) bottle with desiccants placed between the bags and bottle.

The manufacturing process is referenced to DMF [redacted] (b) (4).

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m2. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, [redacted] (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-NOV-2010, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see Microbiology Review). However, there are some issues with the carton and container labeling to correct; see IA.

III. Administrative

This NDA Amendment was submitted in electronic format as a 505(b)(2) application. A Quality Overall Summary is included in the original application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

J.Jee/ONDQA/Reviewer
S.Pope /ONDQA/Branch Chief

C. CC Block

D.Mesmer/ONDQA/Regulatory PM
F.Cross/DDOP/Regulatory PM
H.Sarker/ONDQA/CMC Lead

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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/

JOSEPHINE M JEE
11/22/2010

SARAH P MIKSINSKI
12/13/2010

HARIPADA SARKER
12/15/2010

NDA 22-234

Amendment

Docetaxel Injection

Hospira Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

-

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III. Administrative 11

A. Reviewer's Signature 11

B. Endorsement Block 11

C. CC Block 11

Chemistry Assessment **12**

I. .....Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 12

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S.1 General Information 12
S.2 Manufacture 12
S.3 Characterization 13
S.4 Control of Drug Substance 13
S.5 Reference Standards or Materials 15
S.6 Container Closure System 15
S.7 Stability 15

P DRUG PRODUCT [Docetaxel Injection, Hospira] 15

P.1 Description and Composition of the Drug Product 15
P.2 Pharmaceutical Development 17
P.3 Manufacture 19
P.4 Control of Excipients 30
P.5 Control of Drug Product ..... **Error! Bookmark not defined.**
P.6 Reference Standards or Materials 34
P.7 Container Closure System 35

P.8 Stability 38

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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 46

A. Labeling & Package Insert 46

B. Environmental Assessment or Claim of Categorical Exclusion 52

Chemistry Review Data Sheet

1. NDA 22-234 Amendment

2. REVIEW #2

3. REVIEW DATE: 24-NOV-2009 (first draft); 04-DEC-2009 (final draft)

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	11-JUL-2007
Amendment (BC)	14-MAR-2008
Amendment (BL)	24-APR-2008
Amendment (BC)	08-MAY-2008
Review #1	08-JUL-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BL) – Revised carton and content of labeling	30-JUL-2008
Amendment (BL) – Revised Carton and Container Labels	08-AUG-2008
Amendment (BL) – Updated Labeling	11-AUG-2008
Amendment (RD) – Add Alternate Man. Site for DP	12-JUN-2009
Amendment (BZ) – Add Alternate Man. Site for DP	12-JUN-2009
Amendment – Response to Chemistry Deficiencies	03-DEC-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira Inc.
Address:	275 North Field Dr Dept. 389, Bldg. H2-2 Lake Forest, IL 60045
Representative:	Wendy Tian
Telephone:	224-212-6163

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg/2 mL, 80 mg/8 mL, 160 mg/160 mL

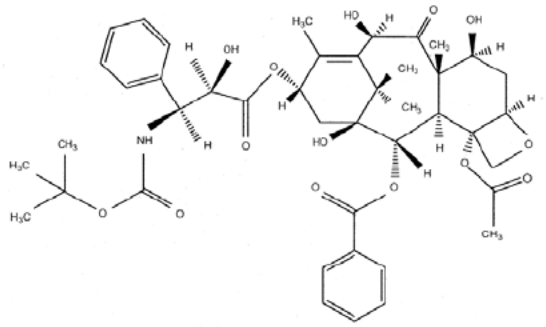
13. ROUTE OF ADMINISTRATION: Injection

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:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



The empirical formula is:

$C_{43}H_{53}NO_{14}$

The molecular weight is 807.88.

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008	By T. Ocheltree
	III			3	Adequate	03-OCT-2007	By J. Chang
	III			3	Adequate	08-JUL-2008	By T. Ocheltree
	V			3	Adequate	03-AUG-2009	By Rona LeBlanc

[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)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		Acceptable	09-DEC-2009
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	09/JUN-2008	Approve as 505(b)(2) / M. Brower	Dr. M. Brower
Biopharm	N/A			
ODS/DMEPA	Labeling consult	04-AUG-2008	Loretta Holmes	Review with comments
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	(b) (4)	06-JUN-2008 24-NOV-2009	Approval (1st cycle) Approval (2nd Cycle)	Dr. A. Lolas (first review cycle) 2nd. Cycle reviewed by B. Riley, Ph.D. 10-DEC-2009

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval with respect to chemistry, manufacturing, and controls (CMC). This is a review for the amendment dated 12-JUN-2009, which provides for an alternate site of drug product manufacture, Zydus Hospira Oncology Private Limited (ZHOPL) and the use of (b) (4) closures at the ZHOPL site. The manufacturing controls, including formulation, components/composition, container/closure system, specification, and analytical methods remain unchanged.

The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in either this review or the review for DMF (b) (4) This also applies to the amendment under review. All CMC comments related to the carton and container labels have either been implemented or satisfactorily addressed. These comments also apply to the amendment dated 12-JUN-2009.

The following comment should be included in the action letter (see CMC review #1):

1. An expiration dating period of 18 months is granted for your product when stored at 25°C/60%RH, protected from light.

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III. Administrative 11

A. Reviewer's Signature 11

B. Endorsement Block 11

C. CC Block 11

Chemistry Assessment **12**

I. .....Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 12

S DRUG SUBSTANCE [Docetaxel, (b) (4)] 12

S.1 General Information 12
S.2 Manufacture 12
S.3 Characterization 13
S.4 Control of Drug Substance 13
S.5 Reference Standards or Materials 15
S.6 Container Closure System 15
S.7 Stability 15

P DRUG PRODUCT [Docetaxel Injection, Hospira] 15

P.1 Description and Composition of the Drug Product 15
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P.4 Control of Excipients 30
P.5 Control of Drug Product ..... **Error! Bookmark not defined.**
P.6 Reference Standards or Materials 34
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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 46

A. Labeling & Package Insert 46

B. Environmental Assessment or Claim of Categorical Exclusion 52

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

None

II. Summary of Chemistry Assessment – See Chemistry Review #1

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Docetaxel injection is formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. Taxotere preparation requires a two-step dilution prior to IV administration, where as the proposed product is added directly to the IV solution. The proposed undiluted docetaxel injection formulation contains the same drug substance (b) (4) as diluted Taxotere (following the initial dilution). The proposed drug product also contains polyethylene glycol 300 (b) (4) and citric acid (b) (4)

(b) (4). It will be marketed as a 10 mg/mL formulation in three packaging configurations (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL) in contrast to the reference listed drug (RLD). The RLD contains 20 or 80 mg of drug formulated in 0.5 ml or 2 ml of polysorbate 80. Additionally, the 80 mg/8 mL, and 160 mg/16 mL presentations are multi-use vials, which is not available for the RLD. All three presentations consist of Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals. The container closure system for the ZHOPL manufacturing site is the same as the original with exception of the (b) (4) stoppers. According to the applicant these presentation were developed based on considerations of patient dose, practitioner convenience, less risk of exposure to toxic compounds, reduced potential for contamination, and less hazardous waste being formed.

The proposed drug product is manufactured by (b) (4) The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A (b) (4) expiry date is proposed based on 12 months of long term and 6 months accelerated stability data. While a (b) (4) expiry was granted in the first review (see Chemistry Review #1), a (b) (4) (18-month) expiry is currently granted for this amendment, due to a decreased amount of data for the newly proposed site.

(b) (4) The maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B) and were consulted to the Pharmacology/Toxicology reviewer for assessment. This information applies to both facility sites, Mulgrave, Australia and Zydus, India.

Drug Substance

Docetaxel is an anhydrous, white to off-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may influence drug product performance and manufacturability. A major (b) (4) impurity (b) (4) is formed by (b) (4). X-ray diffraction has identified (b) (4) morphic forms (b) (4) It is reported that the desired morphic form (b) (4) is produced during manufacture (b) (4).

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in (b) (4) bags, in (b) (4) bottle with desiccants placed between the bags and bottle.

The manufacturing process is referenced to DMF (b) (4).

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m2. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy, the treatment of metastatic, hormone-refractory

prostate cancer in combination with prednisone, (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval. An overall acceptable recommendation was received from the Office of Compliance on 09-DEC-2009, and the microbiology reviewer recommended approval of this amendment on 10-DEC-2009 (see microbiology review).

III. Administrative

This NDA was submitted in both paper and electronic format as a 505(b)(2) application. A Quality Overall Summary is included in the original application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

J.Jee/ONDQA/Reviewer
S.Pope /ONDQA/Branch Chief

C. CC Block

D.Mesmer/ONDQA/Regulatory PM
F.Cross/DDOP/Regulatory PM
T.Ocheltree/ONDQA/PAL

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22234	ORIG-1	HOSPIRA INC	DOCETAXEL INJECTION

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

/s/

JOSEPHINE M JEE
12/10/2009

Sarah Pope Miksinski
12/10/2009

TERRANCE W OCHELTREE
12/10/2009

CHEMISTRY REVIEW

NDA 22-234

Docetaxel Injection

Hospira Inc.

Terrance Ocheltree, R.Ph., Ph.D.

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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Chemistry Review Data Sheet

1. NDA 22-234

2. REVIEW #1

3. REVIEW DATE: 08-JUL-2008

4. REVIEWERS: Terrance Ocheltree, R.Ph., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (CMC)	11-JUL-2007
Amendment (BC)	14-MAR-2008
Amendment (BL)	24-APR-2008
Amendment (BC)	08-MAY-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira Inc.
Address:	275 North Field Dr Dept. 389, Bldg. H2-2 Lake Forest, IL 60045
Representative:	Wendy Tian
Telephone:	224-212-6163

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):

c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg/2 mL, 80 mg/8 mL, 160 mg/160 mL,

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

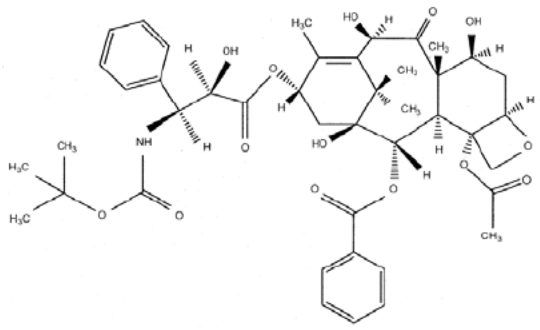
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



The empirical formula is:

$C_{43}H_{53}NO_{14}$

The molecular weight is 807.88.

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	1	Adequate	08-JUL-2008	By T. Ocheltree
	III			3	Adequate	03-OCT-2007	By J. Chang
	III			1	Adequate	08-JUL-2008	By T. Ocheltree

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)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections		Acceptable	20-JUN-2008
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)		Approve as 505(b)(2) / M. Brower	
Biopharm	N/A			
ODS/DMEPA	Labeling consult		Pending	
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	N/A			Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	(b) (4)	06-JUN-2008	Approval / A. Lolas	

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is approval with respect to the chemistry, manufacturing, and controls (CMC). The sites recommendation from the Office of Compliance is listed in EES (attachment 1) as acceptable. The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately respond to all CMC issues outlined in either this review or the review for DMF (b) (4). All CMC comments related to the carton and container labels have either been implemented or satisfactorily addressed.

The following comment should be included in the action letter.

1. An expiration dating period of (b) (4) is granted to your product. You may extend the expiration date based on satisfactory accrual of real time stability data and report it in an annual report.
2. We remind you of your letter dated 11-MAR-2008 in which you have indicated that the (b) (4) has been withdrawn. Therefore, any future site change should be submitted as a prior-approval supplement to the NDA.

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

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Docetaxel injection is formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. Taxotere preparation requires a two-step dilution prior to IV administration, where as the proposed product is added directly to the IV solution. The proposed undiluted docetaxel injection formulation contains the same drug substance, (b) (4) as diluted Taxotere (following the initial dilution). The proposed drug product also contains polyethylene glycol 300 (b) (4) and citric acid (b) (4) It will be marketed as a 10 mg/mL formulation in three packaging configurations (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL) in contrast to the reference listed drug (RLD). The RLD

contains 20 or 80 mg of drug formulated in 0.5 ml or 2 ml of polysorbate 80. Additionally, the 80 mg/8 mL, and 160 mg/16 mL presentations are multi-use vials, which is not available for the RLD. All three presentations consist of Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals. According to the applicant these presentation were developed based on considerations of patient dose, practitioner convenience, less risk of exposure to toxic compounds, reduced potential for contamination, and less hazardous waste being formed.

The proposed drug product is manufactured by (b) (4) The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A (b) (4) expiry date is proposed based on 12 months of long term and 6 months accelerated stability data.

(b) (4) The maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B), but less than the current specifications for the RLD (Taxotere).

Drug Substance

Docetaxel is a anhydrous, white to off-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may influence drug product performance and manufacturability. A major (b) (4) impurity (b) (4) is formed by (b) (4) X-ray diffraction has identified (b) (4) morphic forms that (b) (4) It is reported that the desired morphic form (b) (4) is produced during manufacture (b) (4)

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in (b) (4) bags, in (b) (4) bottle with desiccants placed between the bags and bottle.

The manufacturing process is referenced to DMF (b) (4)

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m2. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approvable for NDA 22-234 is based on the need to resolve labeling issues identified in the Labeling and Package Insert section at the end of this review.

III. Administrative

This NDA was submitted in both paper and electronic (labeling section only) as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

T.Ocheltree/ONDQA/Reviewer
R. Harapanhalli /ONDQA/Branch Chief

C. CC Block

D.Mesmer/ONDQA/Regulatory PM
F.Cross/DDOP/Regulatory PM
S.Pope/ONDQA/PAL

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/s/

Terrance Ocheltree
7/24/2008 05:08:55 PM
CHEMIST

Ravi Harapanhalli
7/24/2008 05:28:49 PM
CHEMIST

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Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-234
Applicant:	Hospira, Inc.
Stamp date:	11-JUL-2007
PDUFA Date:	11-MAY-2008 (standard review anticipated)
Proposed Trade Name:	N/A
Established Name:	Docetaxel Injection
Laboratory Codes:	N/A
Dosage Form:	Injectable
Dosage Strength(s):	20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL
Route of Administration:	Intravenous injection
Indication:	Identical to the indications currently approved for Taxotere/docetaxel (head and neck cancer, hormone-refractory prostate cancer, locally-advanced or metastatic breast cancer, NSCLC, and gastro adenocarcinoma)

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	√	
Draft Comments for 74-Day Letter:		√

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-234 is submitted for Docetaxel Injection, with the proposed indications identical to those currently approved for Taxotere. NDA 22-234 is submitted as a 505(b)(2) application. The reference listed drug is Taxotere (docetaxel) Injection Concentrate, which was approved in 1996. The chemical basis for the 505(b)(2) status is related to the following five points:

- The Applicant's product can be directly diluted into infusion solutions, as compared to the innovator's product, which must be first diluted to a specified concentration prior to dilution into the infusion bag.
- The qualitative and quantitative compositions of the Applicant's product varies from that of the innovator.
- The Applicant is registering an additional presentation (160/16 mL) that the innovator does not have.
- The Applicant proposes a multi-dose application for the 80 mg/8 mL and 160 mg/16 mL presentations, relative to the innovator's product which is supplied as single-dose vials.
- The Applicant's labeling differs from that of the innovator.

Drug Substance Summary

Docetaxel is a white to off-white powder, is freely soluble in polar organic solvents (ethanol, (b) (4)), and is insoluble in water. The structure of docetaxel is presented below (Figure 1). (b) (4) Docetaxel occurs in an anhydrous form, and polymorph screening studies resulted in additional identified morphic forms. The desired morphic form is produced during manufacture (b) (4)

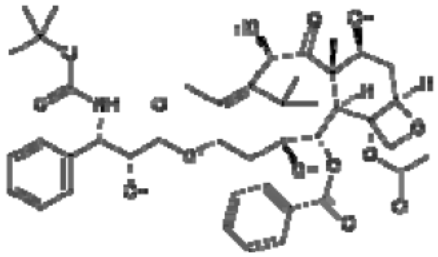

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Figure 1. Docetaxel
MW = 807.88 mg/mmol

All Chemistry, Manufacturing and Controls information for the drug substance has been cross referenced to DMF (b) (4) An acceptable Letter of Authorization has been provided for this cross-reference.

The proposed primary manufacturing site is listed below:

(b) (4)

Once manufactured, the drug substance is tested for appearance, identification (IR and HPLC), optical rotation, assay (HPLC), related substances (HPLC), heavy metals, residue on ignition, residual solvents, bacterial endotoxins (b) (4)

All stability data is located in DMF (b) (4). The Applicant proposes a (b) (4) retest period for the drug substance, presumably when stored at (b) (4) This is not specifically confirmed in the submission.

Drug Product Summary
Docetaxel Injection is formulated as a sterile nonaqueous solution (10 mg/mL). The solution is filled into three vial sizes (20 mg/2 mL, 80 mg/8 mL, and 160 mg/16 mL). The solution is intended for dilution into an infusion solution prior to patient administration. The undiluted formulation contains the API and the following excipients: dehydrated alcohol, citrc acid, polyethylene glycol, polysorbate 80 (b) (4)

Docetaxel Injection is manufactured by (b) (4) The filled vials are tested for description, particulate matter, extractable volume, assay (HPLC), identification (HPLC and TLC), chromatographic purity (HPLC), ethanol content (GC), sterility (USP <71>), and bacterial endotoxins (USP <85>). Docetaxel Injection is packaged into Type I clear glass vials fitted with gray (b) (4) rubber stoppers and flip-off aluminum seals.

The proposed manufacturing sites are listed below:

Manufacturing
Mayne Pharma Limited
1 Lexia Place, Mulgrave
3170 Victoria
Australia
FEI# 3001174929

The Applicant provides long term (25°C/60% RH; 36 months) and accelerated (40°C/75% RH, 6 months) stability data for five registration batches of Docetaxel Injection, incorporating all three vial sizes, when stored in both inverted and upright positions. The Applicant provides a decreased amount of stability data for the intermediate vial size, based on a bracketing scheme proposed under ICH Q1E. The Applicant's stability package is supplemented with infusion solution in-use and compatibility data, as well as multi-dose stability testing.

The Applicant proposes a (b) (4) expiration dating period for the solution, when stored under room temperature conditions (between 20 and 25°C) and protected from light.

B. Critical issues for review and recommendation

Drug Substance

a. The Applicant proposes direct dilution of the drug product into an infusion bag. While this strategy may alleviate some of the complications associated with multiple sequential dilutions, previously-generated stability data for docetaxel may be less supportive than for the innovator product. The Applicant's entire drug substance stability program should be carefully assessed for adequacy, which is also relevant to its relation to drug product and final infusion solution stability.

b. The Applicant cross-references a Type II DMF for docetaxel manufacture. This DMF should be assessed for adequacy to support this NDA.

c. Docetaxel is known to exhibit polymorphism. The Applicant's ability to consistently produce a quality and specific morphic form of the drug substance should be confirmed during the review.

Drug Product

a. This application requires a consult to the Office of Microbiology for the assessment of all aseptic and microbiological attributes, specifications, and manufacturing process details. The assigned microbiology reviewer should also be consulted for partial review of the proposed (b) (4)

b. The Applicant proposes a (b) (4) for the drug product. The review of this proposal will require tandem reviews by both the assigned CMC and microbiology reviewers.

c. The Applicant's stability package incorporates a multi-dose option for the drug product. This is unique from the innovator product and should, therefore, be carefully evaluated for acceptability based on the available literature and stability data. The Applicant also provides a bracketing scheme based on ICH Q1E. This should also be carefully addressed for adequacy, as the multiple vial sizes are unique to the current NDA.

d. The Agency has recently identified several significant safety concerns regarding the container/carton labeling for the innovator product (Taxotere). While the current NDA circumvents one dilution step in its preparation, the potential applicability (or non-applicability) of Taxotere-related labeling issues should be confirmed as part of the container/carton labeling review.

C. Comments for 74-day Letter:

None.

D. Recommendation for Fileability: Fileable

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	 √ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMETS/ODS EER

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
(b) (4)			Yes
			Yes
			Yes

Recommendation for Team Review:

This NDA does not include a significant amount of drug substance information, as most Chemistry, Manufacturing and Controls information is cross-referenced to DMF (b) (4) The drug product is a fairly standard injectable formulation.

The team review approach is not recommended for this NDA. This is a conventional dosage form with typical review issues anticipated during the CMC review. This review should be easily accomplished by a single CMC reviewer.

Sarah C. Pope, Ph.D. — 14-AUG-2007
Pharmaceutical Assessment Lead — Date

Ravi Harapanhalli, Ph.D. — 14-AUG-2007
Branch Chief — Date

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/s/

Sarah Pope
9/6/2007 05:12:28 PM
CHEMIST

Ravi Harapanhalli
9/6/2007 08:20:40 PM
CHEMIST
Bullet # 2 on first page of the review should clarify that the variation in qualitative and quantitative compositions from RLD is only with regard to excipients and (b) (4). The drug content remains the same as it is in the RLD.