

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200795Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 200-795**  
**CMC Review # 3****Gemcitabine Injection**

200 mg/5.3 ml, 1 g/26.3 ml & 2 g/52.6 ml  
(as free base Gemcitabine)

**Hospira, Inc.****Akm Khairuzzaman, Ph.D.**

Review Chemist

**Office of New Drug Quality Assessment**  
**Division of New Drug Quality Assessment I**  
Branch II

**CMC REVIEW OF NDA 200-795**  
**For the Division of Drug Oncology Products (HFD-150)**

## Chemistry Review Data Sheet

1. NDA 200-795
2. REVIEW #: 3
3. REVIEW DATE: 08/02/2011
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC review by Dr. Joyce Crich	12/15/2010
Akm Khairuzzaman	07/15/2011

6. SUBMISSION(S) BEING REVIEWED: N/A
7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Hospira, Inc
<b>Address</b>	275 North Field Drive Dept. 0389, Bldg H2 Lake Forest, IL 60045-5046
<b>Representative</b>	Khaled M. Mohamed
<b>Telephone</b>	224-212-4909
<b>FAX Number</b>	N/A

8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	None
<b>Non-Proprietary Name (USAN)</b>	Gemcitabine Injection
<b>Code Names</b>	N/A
<b>Chemistry Type</b>	3
<b>Submission Priority</b>	Resubmission, Class 1

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

## Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Indicated for the first-line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic non-small cell lung cancer, and locally advanced or metastatic adenocarcinoma of the pancreas.

11. DOSAGE FORM: Sterile solution, injection

12. STRENGTH/POTENCY: 38 mg/mL (as free base Gemcitabine)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

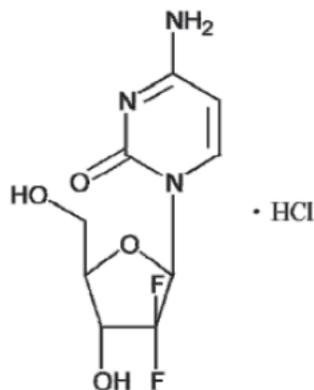
2'-Deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -isomer) Cytidine: 2'-deoxy-2',2'-difluoro-, monohydrochloride (United States Pharmacopoeia Chemical Name)

Or

4-Amino-1-(2-deoxy-2,2'-difluoro- $\beta$ -D-erythro-pentofuranosyl)pyrimidin-2(1H)-one, hydrochloride (European Pharmacopoeia Chemical Name)

US Adopted Name (USAN): Gemcitabine

Chemical structure:



## Chemistry Review Data Sheet

Chemical Formula:

 $C_9H_{11}F_2N_3O_4 \cdot HCl$ 

Molecular Weight:

299.7 (hydrochloride)

(b) (4)

## Chemistry Review Data Sheet

## 17. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CMC	Acceptable	07/15/2011	Akm Khairuzzaman, Ph.D.
Biometrics	N/A	N/A	
EES	Withhold	06-DEC-2010	April Inyard
	Acceptable	22-JULY-2011	April Inyard
Pharm/Tox	Not Approval	08-DEC-2010	Robert Dorsam
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA	Pending	24-SEP-2010	Yelena L Maslov
EA	Categorical Exclusion: Acceptable	06-DEC-2010	Joyce Z Crich
Microbiology	Approval	13-SEP-2010	Stephen E Langille
	Approval – labeling deficiency outlined in 02-DEC-2010 memo	22-NOV-2010	Stephen E Langille
Biopharmaceutics	Grant the request for a waiver of the <i>in vivo</i> study	02-FEB-2010	Tapash K Ghosh

## The Chemistry Review for NDA 200-795

### The Executive Summary

The CMC reviewer, Dr. Akm Khairuzzaman has already made recommendation on this NDA as “Approvable” in the review dated 07/15/2011 based on the analytical method validation update. However, such review has not made any conclusion on the expiration date because the only deficiency that was communicated to the sponsor by the first CMC review Dr. Joyce Crich (dated 12/15/2010) was the insufficient analytical method validation. Therefore, the decision on the product’s shelf life of 18 months was pending (Dr. Joyce Crich, CMC review # 1, dated 12/15/2010, page # 135 of 141). Under CMC review # 2, since Dr. Akm Khairuzzaman has found that the analytical method validation was satisfactory, the shelf life of 18 months can be approved.

**Recommended product shelf life:** 18 months at refrigerated storage conditions.

### Administrative

#### A. Reviewer’s Signature

/s/ A. Khairuzzaman, Ph.D., Reviewer, ONDQA.

#### B. Endorsement Block

Chemistry Reviewer:  
Pharmaceutical Assessment Lead:  
Branch Chief:

Akm Khairuzzaman, Ph.D.  
Haripada Sarker, Ph.D.  
Sarah Pope Miksinski, Ph.D.

#### C. CC Block

Orig. NDA 200-795  
Entered electronically in DFS

**Final Recommendation:** This NDA can be recommended for approval from the perspective of chemistry, manufacturing, and controls.

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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.**  
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/s/  
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AKM KHAIRUZZAMAN

08/02/2011

Recommended product shelf life: 18 months at refrigerated storage conditions.

HARIPADA SARKER

08/03/2011

**NDA 200-795**  
**CMC Review # 2**

**Gemcitabine Injection**  
200 mg/5.3 ml, 1 g/26.3 ml & 2 g/52.6 ml  
(as free base Gemcitabine)

**Hospira, Inc.**

**Akm Khairuzzaman, Ph.D.**  
Review Chemist

**Office of New Drug Quality Assessment**  
**Division of New Drug Quality Assessment I**  
Branch II

CMC REVIEW OF NDA 200-795  
**For the Division of Drug Oncology Products (HFD-150)**

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# Chemistry Review Data Sheet

1. NDA 200-795
2. REVIEW #: 2
3. REVIEW DATE: 07/15/2011  
Revised:
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC review by Dr. Joyce Crich	12/15/2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission/Class 1	06/10/2011

7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Hospira, Inc
<b>Address</b>	275 North Field Drive Dept. 0389, Bldg H2 Lake Forest, IL 60045-5046
<b>Representative</b>	Khaled M. Mohamed
<b>Telephone</b>	224-212-4909
<b>FAX Number</b>	N/A

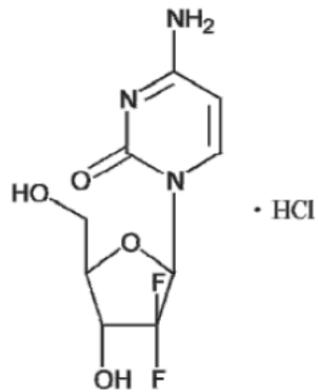
8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	None
<b>Non-Proprietary Name (USAN)</b>	Gemcitabine Injection
<b>Code Names</b>	N/A
<b>Chemistry Type</b>	3
<b>Submission Priority</b>	Resubmission, Class 1

## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Indicated for the first-line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic non-small cell lung cancer, and locally advanced or metastatic adenocarcinoma of the pancreas.
11. DOSAGE FORM: Sterile solution, injection
12. STRENGTH/POTENCY: 38 mg/mL (as free base Gemcitabine)
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
- 2'-Deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -isomer) Cytidine: 2'-deoxy-2',2'-difluoro-, monohydrochloride (United States Pharmacopoeia Chemical Name)  
Or  
4-Amino-1-(2-deoxy-2,2'-difluoro-b-D-erythro-pentofuranosyl)pyrimidin-2(1H)-one, hydrochloride (European Pharmacopoeia Chemical Name)
- US Adopted Name (USAN): Gemcitabine  
Chemical structure:

## Chemistry Review Data Sheet



Chemical Formula:  
Molecular Weight:

$\text{C}_9\text{H}_{11}\text{F}_2\text{N}_3\text{O}_4 \cdot \text{HCl}$   
299.7 (hydrochloride)  
(b) (4)

## Chemistry Review Data Sheet

## 17. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	
EES	Withhold	06-DEC-2010	April Inyard
	Acceptable	22-JULY-2011	April Inyard
Pharm/Tox	Not Approval	08-DEC-2010	Robert Dorsam
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA	Pending	24-SEP-2010	Yelena L Maslov
EA	Categorical Exclusion: Acceptable	06-DEC-2010	Joyce Z Crich
Microbiology	Approval	13-SEP-2010	Stephen E Langille
	Approval – labeling deficiency outlined in 02-DEC-2010 memo	22-NOV-2010	Stephen E Langille
Biopharmaceutics	Grant the request for a waiver of the <i>in vivo</i> study	02-FEB-2010	Tapash K Ghosh

# The Chemistry Review for NDA 200-795

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (200-795) can be recommended for approval from the perspective of chemistry, manufacturing, and controls.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities.

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

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

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

A brief description of the drug substance and the drug product can be found in the original CMC review conducted by Dr. Joyce Crich (dated 12/15/2010) in DARRTS. No deficiencies were identified for the drug substance. For the drug product, the major CMC information such as formulation composition, manufacturing process and control, drug product specification, batch analysis data, stability studies and data, packaging configuration were acceptable by the first CMC reviewer. However, the following deficiencies were identified by Dr. Joyce Crich (dated 12/15/2010) and recommended for not approval which were communicated to the sponsor through a CR letter.

*Method Number (Method No. 6.320 for Chromatographic Purity Test) is not adequately validated for **linearity**, **accuracy**, and **precision**. Accordingly, it is not possible to confirm actual levels of the following impurities in supporting and primary drug product batches:*

*(b) (4)*

On June 10, 2011 the applicant resubmitted the NDA along with the details of the analytical method (chromatographic purity test, method #6.320). The sponsor has revalidated this method for linearity, accuracy, and precision at the proposed limits and at the higher concentrations of impurities (namely: *(b) (4)*) utilized in the non-clinical toxicology studies. The details of these individual validation test method, criteria and data are discussed in the later part of this review. The level of these impurity that were used

## Executive Summary Section

in the non-clinical study for qualification purpose were questionable due to fact that the analytical method validation information was not submitted in the original submission. Resubmission of this application has provided enough information on validation of the HPLC method that demonstrates that the method is specific, accurate, linear, sensitive and precise over the ICH range of QL to 120% of specification. Additionally, the validation testing was also conducted over an extended range (beyond the ICH guideline) to accommodate the batches with high levels of these impurities used in the toxicological studies. The results demonstrated that the method is accurate, precise and linear over the extended range. Therefore, the qualification level of these impurity derived from the non clinical studies are now acceptable.

A list of labeling deficiencies are identified at the end of this review which will be sent out to the sponsor and these issues can be addressed during the course of labeling follow up meetings. Other than that this application can be approved from CMC point of view.

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

Can be found in Review # 1.

**C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (200-795) **can be approved** from the perspective of chemistry, manufacturing, and controls. The applicant has adequately re-submitted the required information (HPLC purity test, method number 6.320) in response to the identified CMC deficiencies communicated through the CR letter.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

/s/ A. Khairuzzaman, Ph.D., Reviewer, ONDQA.

**B. Endorsement Block**

Chemistry Reviewer:

Akm Khairuzzaman, Ph.D.

Pharmaceutical Assessment Lead:

Haripada Sarker, Ph.D.

Branch Chief:

Sarah Pope Miksinski, Ph.D.

**C. CC Block**

Orig. NDA 200-795

Entered electronically in DFS

16 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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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.**  
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/s/  
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AKM KHAIRUZZAMAN

07/15/2011

This NDA can be approved from CMC point of view

HARIPADA SARKER

07/15/2011

# **NDA 200795**

## **Gemcitabine Injection**

**Hospira, Inc**

**Joyce Z Crich, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment I  
Branch II**

**CMC REVIEW OF NDA 200795  
For the Division of Drug Oncology Products (HFD-150)**

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1. NDA 200795
2. REVIEW #: 1
3. REVIEW DATE: 20-NOV-2010
4. REVIEWER: Joyce Crich, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents

(b) (4)  
IND 106215

Document Date

01-May-2009  
24-Sep-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	SN0000	11-DEC-2009
Amendment	SN0001	19-JAN-2010
Amendment (Response to 02-JUL-2010 CMC IR)	SN0006	03-AUG-2010
Amendment (Response to 02-JUL-2010 CMC IR)	SN0007	05-AUG-2010
Amendment (Response to 27-JUL-2010 CMC IR)	SN0008	16-AUG-2010
Amendment (Response to 21-OCT-2010 CMC IR)	SN0010	29-OCT-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Hospira, Inc  
 Address: 275 North Field Drive  
 Dept. 0389, Bldg H2  
 Lake Forest, IL 60045-5046  
 Representative: Khaled M. Mohamed  
 Telephone: 224-212-4909

## CMC Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Gemcitabine Injection
- b) Non-Proprietary Name (USAN): Gemcitabine:
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: 5

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

## 10. PHARMACOL. CATEGORY: Indicated for the first-line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic non-small cell lung cancer, and locally advanced or metastatic adenocarcinoma of the pancreas.

## 11. DOSAGE FORM: Sterile solution, injection

## 12. STRENGTH/POTENCY: 38 mg/mL (as free base Gemcitabine)

## 13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

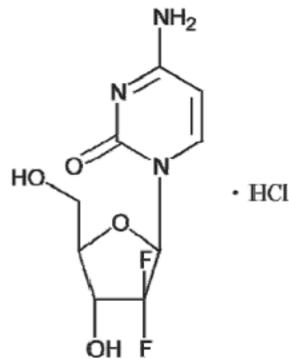
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2'-Deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -isomer) Cytidine: 2'-deoxy-2',2'-difluoro-, monohydrochloride (United States Pharmacopoeia Chemical Name)

Or

4-Amino-1-(2-deoxy-2,2'-difluoro-b-D-erythro-pentofuranosyl)pyrimidin-2(1H)-one, hydrochloride (European Pharmacopoeia Chemical Name)

CMC Review Data Sheet



Molecular Formula: C<sub>9</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>·HCl

Molecular Weight: 299.7 (hydrochloride)

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TY PE	HOLDER	ITEM REFEREN CED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Reviewed by Terrance Ocheltree on 03/17/2008	
	III			3	Adequate	Reviewed by Sheldon Markofsky on 08/13/2010	
	III			3	Adequate	Reviewed by Zedong Dong on 06/18/2009	

<sup>1</sup> 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")

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

CMC Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	106215	IND for development

(b) (4)

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	
EES	Withhold	06-DEC-2010	April Inyard
Pharm/Tox	Not Approval	08-DEC-2010	Robert Dorsam
Biopharm	Grant the request for a waiver of the <i>in vivo</i> study	02-FEB-2010	Tapash K Ghosh
LNC	N/A		
Methods Validation	N/A	N/A	
DMEPA	Pending	24-SEP-2010	Yelena L Maslov
EA	Approval	06-DEC-2010	Joyce Z Crich
Microbiology	Approval	13-SEP-2010	Stephen E Langille
Microbiology	Approval – labeling deficiency outlined in 02-DEC-2010 memo	22-NOV-2010	Stephen E Langille

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 200795

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval from a chemistry, manufacturing, and controls (CMC) standpoint until the following deficiency is satisfactorily resolved:

Method Number (Method No. 6.320 for Chromatographic Purity Test) is not adequately validated for linearity, accuracy, and precision. Accordingly, it is not possible to confirm actual levels of the following impurities in supporting and primary drug product batches: (b) (4)

Additionally, the Office of Compliance has issued an overall withhold recommendation (06-DEC-2010) for this application. This application cannot be recommended for approval until the above deficiency and any cGMP-related deficiencies are satisfactorily resolved.

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

None

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

The drug substance Gemcitabine Hydrochloride is named as 2'-Deoxy-2',2'-difluorocytidine monohydro-chloride ( $\beta$ -isomer) Cytidine: 2'-deoxy-2', 2'-difluoro-, monohydrochloride (CAS# 122111-03-9). Its alternate chemical name is 4-Amino-1-(2-deoxy-2, 2'-difluoro-b-D-erythro-pentofuranosyl) -pyrimidin-2(1H)-one hydrochloride. The USAN and INN is Gemcitabine Hydrochloride. It has a molecular weight of 299.7 (hydrochloride) (b) (4) and the molecular formula is  $C_9H_{11}F_2N_3O_4.HCl$ . Its appearance is white to off-white powder with a melting point of 287 – 292 °C. Gemcitabine Hydrochloride is soluble in water, slightly soluble in ethanol, and is insoluble in chloroform and acetone. Its Specific Optical Rotation is  $[\alpha]_D = + 43^\circ$  to  $+ 50^\circ$  (10 mg/mL at 20°C).

## Executive Summary Section

The process of manufacturing Gemcitabine Hydrochloride involves (b) (4)

The manufacturing of Gemcitabine Hydrochloride will be performed at the following sites based on the stages of manufacturing process: (b) (4)

(b) (4) sites are responsible for production, testing and release of the drug substance.

The provided long-term drug substance stability data support a (b) (4) retest period under storage conditions of  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  ( $60\% \pm 5\%\text{RH}$ ). The stability data show no trend for increasing degradants for up to 24 months under long-term stability conditions and for up to 6 months under accelerated conditions ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ,  $75\% \pm 5\%\text{RH}$ ).

There are no remaining CMC deficiencies related to drug substance.

## (2) Drug Product

Gemcitabine Injection is supplied as single-use vials with (b) (4) capacities capped with a grey (b) (4) closure and an aluminum seal with plastic flip-off top. The vials contain 200 mg/5.3 mL, 1 g/26.3 mL, and 2 g/52.6 mL respectively. The secondary packaging consists of a clear plastic sleeve, or (b) (4) protection, over the final labeled sealed container and a carton box. Gemcitabine Injection is a sterile concentrated aqueous solution (38 mg/mL) with a pH range of 2.0 – 3.0, intended to be diluted with 0.9% NaCl to concentrations as low as 0.1 mg/mL prior to intravenous administration. Gemcitabine Injection is formulated as 38 mg (free base Gemcitabine)/mL in Water for Injection, with Hydrochloric Acid and/or Sodium Hydroxide used for pH adjustment. All excipients meet the current USP compendial standards. As the Applicant states in section P. 2, the only difference from the RLD (Gemzar) is the omission of mannitol, sodium acetate and sodium chloride, which were part of the RLD formulation. The Applicant claims that “Stability studies show the pH of the drug product does not change during storage at either 2 – 8 °C (the proposed storage condition) or 25°C (accelerated storage condition); (b) (4) (b) (4) However, the stability study results (discussed herein in 3.2.P.8) indicate a trend of increasing levels of degradants.

The proposed commercial drug product is manufactured by Hospira Australia Pty. Ltd (Mulgrave, Victoria, Australia). The manufacturing process (b) (4)

The drug product manufacturing process was changed (b) (4)

## Executive Summary Section

(b) (4) The proposed commercial batch scale is (b) (4)

The drug solution is filled into Type I glass vials (b) (4) respectively) and stoppered with (b) (4) type closures (b) (4) grey). The suitability of the proposed closure system with Gemcitabine Injection was supported by extractables/leachables data from a stability study. The dilution compatibility and stability of Gemcitabine Injection were also assessed with admixes of 0.9% Sodium Chloride Injection (b) (4). The diluted drug has been shown to be compatible with both 0.9% Sodium Chloride (b) (4) in the PVC infusion bags, and is stable for up to 24 hours at the concentration between 0.1 – 26 mg/mL in 0.9% Sodium Chloride (b) (4).

The proposed drug product specifications are typical for small volume parenteral drug products to be used for IV administration. They include appearance, identification, pH, assay, impurities, and volume in container, particulate matter, residual solvents, sterility, and bacterial endotoxins. There are five specified impurities that are present in the drug product batches with the acceptance limits as revised in 3-Aug-2010 amendment as (b) (4)

(b) (4) which are higher than the ICHQ3B recommended maximum qualification thresholds (0.15-0.2%), except for (b) (4). The proposed acceptance limits for those degradants and impurity were consulted to the Pharmacology/Toxicology review team. The proposed acceptance limits for (b) (4) were found to be acceptable based on the qualification levels in non-clinical tox studies (refer to Dr. Robert Dorsam's Pharmacology/Toxicology review dated 08-DEC-2010). However, the analytical methods for measuring impurities (b) (4) are neither validated nor adequately validated in terms of linearity, accuracy, and precision. The Relative Response Factor (RRF)'s determinations for impurities (b) (4) in the HPLC method need to be reconfirmed. Therefore, the batch analysis data for impurity levels in drug product for the five registration batches (including the lot U022750RA after being used in forced degradation studies and then used in non-clinical toxicology studies) are not necessarily accurate based on the invalid analytical methods. As a consequence: (i) the proposed acceptance criteria for these impurities in the drug product specifications are not necessarily based on acceptable batch data; (ii) the proposed 18 month expiration dating period is not adequately supported by valid batch analysis data; and (iii) the qualification levels of these impurities in non-clinical tox studies are only relatively but not absolutely defined. Also refer to the separate but related deficiency outlined in the Pharmacology/Toxicology review (08-DEC-2010).

Hospira proposes an 18-month shelf life for Gemcitabine Injection when stored at 2-8°C based upon the stability data from 24 months of 5 primary stability batches at 5+/-3°C (long term conditions). The stability data showed a trend of increasing levels of

## Executive Summary Section

degradants (total, and each specified impurities, though within the proposed release specifications) under long term conditions. Based on the previously-noted CMC deficiency, it is not possible to confirm a shelf life at this time due to the ambiguity present in the stated batch analysis (particularly with regard to impurity levels). Once acceptable methodology has been developed and submitted, an expiration dating period can be confirmed.

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

Gemcitabine Injection is supplied as single-use vials with [REDACTED] (b) (4) capacities containing 200 mg/5.3 mL, 1 g/26.3 mL, and 2 g/52.6 mL, respectively. Gemcitabine Injection is a sterile concentrated aqueous solution (38 mg/mL) with a pH range of 2.0 – 3.0 to be diluted with 0.9% NaCl to concentrations as low as 0.1 mg/mL prior to intravenous administration.

Gemcitabine is a nucleoside metabolic inhibitor indicated for:

- Ovarian Cancer in combination with carboplatin
- Breast Cancer in combination with paclitaxel
- Non-Small Cell Lung Cancer in combination with cisplatin
- Pancreatic Cancer as a single agent

The recommended dose of Gemcitabine Injection is as follows:

- Ovarian: 1000 mg/m<sup>2</sup> over 30 minutes on Day 1 and 8 of each 21-day cycle
- Breast Cancer: 1250 mg/m<sup>2</sup> over 30 minutes on Day 1 and 8 of each 21-day cycle
- Non-Small Cell Lung Cancer: 4-week schedule, 1000 mg/m<sup>2</sup> over 30 minutes on Days 1, 8, and 15 of each 28-day cycle; 3-week schedule; 1250 mg/m<sup>2</sup> over 30 minutes on Days 1 and 8 of each 21-day cycle
- Pancreatic: 1000 mg/m<sup>2</sup> over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks
- Dose Reductions or discontinuation may be needed based on toxicities

**C. Basis for Approvability or Not-Approval Recommendation**

Method Number 6.320 (Chromatographic Purity Test) is not adequately validated for linearity, precision, and accuracy. Therefore, all generated batch data can not be confirmed as acceptable and accurate in support of the proposed specifications and expiration dating period.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Joyce Crich, Ph.D, Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Liang Zhou, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

**C. CC Block:** entered electronically in DFS

129 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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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.**  
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/s/  
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JOYCE Z CRICH  
12/14/2010

SARAH P MIKSINSKI  
12/15/2010



## Background Summary

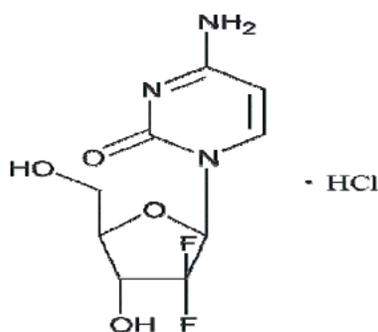
This application was originally submitted under (b) (4) which was withdrawn after a Refuse to File Letter was sent due to insufficient stability data. This application proposes the drug product, Gemcitabine Injection, for the treatment of first-line metastatic breast cancer, ovarian cancer, locally advanced or metastatic non-small cell lung cancer, and locally advanced or metastatic adenocarcinoma of the pancreas. A gemcitabine lyophilized formulation, Gemzar® was previously approved by the Agency under NDA 20-509. The proposed drug product contains the same active ingredient at the same concentration Reference Listed Drug (RLD), Gemzar®, after reconstitution. The excipients are the same as those used in the RLD except for the removal of mannitol and sodium acetate. The proposed drug is formulated as an aqueous solution in three different strengths, 200 mg, 1 gm and 2 gm with concentration upon reconstitution of 38 mg/mL. The 2 gm/52.6 mL configuration is a new configuration not currently marketed by the innovator.

The applicant references a Pre-Investigational New Drug Application (IND) meeting request. The meeting was cancelled by the applicant after responses were provided by the Agency.

## Drug Substance (DS)

The applicant provides full drug substance information in the submission. (b) (4) manufacturing sites (b) (4) have been proposed. (b) (4)

Gemcitabine is an optically active compound with a beta-isomer and is synthesized as its hydrochloride salt. Gemcitabine hydrochloride is soluble in water at 10 mg/mL in pH range of 2-3. Two drug substance structurally-related impurities are indicated in the submission. An Establishment Evaluation Request was submitted to the Office of Compliance to evaluate cGMP compliance for the drug substance manufacturing sites listed in the submission. The drug substance is identified with following structure.



Based on six months accelerated and up to 24 months long term stability data on three commercial and three pilot batches, applicant proposes a (b) (4) retest period for the drug substance. Acceptance criteria for drug substance stability are found to be identical to the corresponding acceptance criteria for drug substance release specification.

## Drug Substance Critical Issues

- (b) (4)

- Intermediate specifications should be reviewed for adequacy.
- It should be determined if acceptance testing is required for the intermediate (b) (4)
- The drug substance impurities should be justified as per ICHQ3A. Any new impurity above the ICH qualification level should be justified by literature reference or by additional pre-clinical studies as appropriate. The CMC reviewer should alert the Pharmacology/Toxicology reviewer regarding any impurities present at levels about those stated in ICH Q3A.
- The drug substance stability profile and the proposed (b) (4) retest period should be critically evaluated because different impurity profiles may exist due to variation of manufacturer and manufacturing process.

### Drug Product (DP)

The finished drug product, Gemcitabine Injection, is proposed as a sterile aqueous solution, which is intended for intravenous use. The drug product requires dilution prior to administration. The single dose (b) (4) are (b) (4) with 5.3 mL fill, (b) (4) with 26.3 mL fill, and (b) (4) with 52.6 mL fill, closed with (b) (4) grey (b) (4) closures and aluminum seals with plastic flip-off tops. The composition of the drug product consists of the active ingredient, gemcitabine hydrochloride, as well as inactive ingredients (USP/NF), water for injection prepared with the aid of hydrochloric acid and/or sodium hydroxide for pH adjustment. The pH range is 2.0 to 3.0. This product is sterilized (b) (4) and contains no antimicrobial preservatives.

A comparative composition between the RLD and the drug product of this submission is provided. The applicant states that development was based on the RLD to develop Docetaxel injection and that emphasis was placed on optimizing drug solubility, stability and pH. Impurity (b) (4) is not detected in the RLD product until reconstituted.

The proposed drug product manufacturing site is:

Hospira Australia Pty Ltd,  
1 Lexia Place, Mulgrave,  
Victoria 3170, Australia

Accelerated stability (25°C/60% RH) at 0, 1, 2, 3 and 6 months, and long term stability (5 ± 3°C) data at 0, 3, 6 and 12 months are provided for the drug product packaged in the proposed 10 mL, 30 mL and 100 mL packaging configurations with the (b) (4) closure. Acceptance criteria for drug product stability are found to be identical to the corresponding acceptance criteria for drug product release specification. The following Table provides an overview of the drug product stability protocol.

Strength	Container/Closure	Conditions	Sample Times	Batches
200 mg/5.3 mL	(b) (4)	25°C/60% RH	0, 1, 2, 3 and 6 months	U012750RA
		5 ± 3°C	0, 3, 6, 9, 12, 18 and 24 months	U022750RA
25°C/60% RH		0, 1, 2, 3 and 6 months	U012751RA	
5 ± 3°C		0, 3, 6, 9, 12, 18 and 24 months	U022751RA	
25°C/60% RH		0, 1, 2, 3 and 6 months	U012752RA	
5 ± 3°C		0, 3, 6, 9, 12, 18 and 24 months		

Bracketing was applied on stability batches as per the design in the following Table.

Presentation	200 mg/5.3 mL	1 gm/26.3 mL	2 gm/52.6 mL
Number of batches	2	2	1

Stability profiles for both Gemcitabine Injection concentrate and the infusion solution are provided in normal saline and 5% dextrose at room temperature over 24 hours.

The applicant proposes (b) (4) shelf-life for gemcitabine injection stored at 2°C to 8°C (36 to 46 °F) based on 12 months stability data. The level of (b) (4) exceeded specifications when stored under 6 months accelerated and 12 months intermediate conditions. Statistical analysis is not provided to support the proposed drug product expiration dating. ,

#### *Drug Product Critical Issues*

- There appear to be new degradants in the drug product concentrate (finished dosage form) and infusion solution, relative to those specified in the RLD specification.
- Proposed limits and justification for impurity (b) (4) should be evaluated.
- The DMFs for drug product container/closure systems need to be reviewed for adequacy.
- The bracketing used for stability should be evaluated.
- Determine if the 12 months stability of data is sufficient to support the proposed (b) (4) expiration and whether ICH Q1E can be applied for this extrapolation is a review issue.
- The proposed labeling, which is submitted in PLR (physician's labeling rule) format, needs to be evaluated for its relevant CMC sections.

### 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?		√	Only 12 months DP stability provided
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)	√      √  √ √		<b>Microbiology</b> Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMEPA/OSE <b>EER</b>

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

DMF Number	Holder	Description	LOA Included

**Comments and Recommendations**

The application is fileable. Facilities are being entered into EES for inspection. A team review is not recommended for this NDA, because the drug substance and drug product manufacturing processes are not complex.

**Comment for 74-days letter:**

None

Terrance Ocheltree, R.Ph., Ph.D.  
Pharmaceutical Assessment Lead (PAL)

January 24, 2009  
Date

Sarah Pope Miksinski, Ph.D.  
Branch Chief

January 24, 2009  
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200795	ORIG-1	HOSPIRA INC	GEMCITABINE INJECTION (38MG/ML)

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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.**

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/s/

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TERRANCE W OCHELTREE  
01/27/2010

Sarah Pope Miksinski  
01/29/2010

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 200795/000	<b>Sponsor:</b>	HOSPIRA INC
<b>Orig. Code:</b>	150		275 NORTH FIELD DR DEPT 0389 BLDG H2 2
<b>Priority:</b>	3		LAKE FOREST, IL 60045
<b>Stamp Date:</b>	11-DEC-2009	<b>Brand Name:</b>	GEMCITABINE INJECTION (38MG/ML)
<b>PDUFA Date:</b>	10-AUG-2011	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	GEMCITABINE INJECTION (38MG/ML)
<b>District Goal:</b>	12-AUG-2010	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	

001; INJECTABLE; GEMCITABINE; 200MG/5.3ML  
002; INJECTABLE; GEMCITABINE; 1GM/26.3ML  
003; INJECTABLE; GEMCITABINE; 2GM/52.6ML

<b>FDA Contacts:</b>	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	A. KHAIRUZZAMAN	Review Chemist	(HFD-800)	301-796-3886
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

<b>Overall Recommendation:</b>	ACCEPTABLE	on 22-JUN-2011	by E. JOHNSON	(HFD-320)	301-796-3334
	PENDING	on 20-JUN-2011	by EES_PROD		
	PENDING	on 20-JUN-2011	by EES_PROD		
	WITHHOLD	on 06-DEC-2010	by A. INYARD	()	
	ACCEPTABLE	on 09-FEB-2010	by A. INYARD	()	

**Establishment:**      **CFN:** 9610999      **FEI:** 3001174929  
HOSPIRA AUSTRALIA PTY  
1-23 LEXIA PLACE  
MULGRAVE NORTH, VICTORIA, AUSTRALIA

**DMF No:**      **AADA:**

**Responsibilities:**      DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE LABELER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER  
FINISHED DOSAGE STERILITY TESTER

**Profile:**      STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS      **OAI Status:**      NONE

**Last Milestone:**      OC RECOMMENDATION

**Milestone Date:**      22-JUN-2011

**Decision:**      ACCEPTABLE

**Reason:**      DISTRICT RECOMMENDATION



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	NDA 200795/000	<b>Action Goal:</b>		
<b>Date:</b>	11-DEC-2009	<b>District Goal:</b>	12-AUG-2010	
<b>Regulatory:</b>	11-OCT-2010			
<b>Applicant:</b>	HOSPIRA INC	<b>Brand Name:</b>		
	275 NORTH FIELD DR DEPT 0389 BLDG H2 2	<b>Estab. Name:</b>		
	LAKE FOREST, IL 60045	<b>Generic Name:</b>	GEMCITABINE INJECTION (38MG/ML)	
<b>Priority:</b>	3	<b>Product Number; Dosage Form; Ingredient; Strengths</b>		
<b>Org. Code:</b>	150		001; INJECTABLE; GEMCITABINE; 200MG/5.3ML	
			002; INJECTABLE; GEMCITABINE; 1GM/26.3ML	
			003; INJECTABLE; GEMCITABINE; 2GM/52.6ML	
<b>Application Comment:</b>	505(B)(2). REVIEW CLOCK EXTENDED. PDUFA DATE 1/11/2011 (on 15-OCT-2010 by D. MESMER (HFD-800) 301-796-4023)			
<b>FDA Contacts:</b>	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	J. CRICH	Review Chemist		301-796-3882
	T. OCHELTREE	Team Leader	(HFD-800)	301-796-1988

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<b>Overall Recommendation:</b>	WITHHOLD	on 06-DEC-2010	by A. INYARD	()
	ACCEPTABLE	on 09-FEB-2010	by A. INYARD	()

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 9610999 FEI: 3001174929

HOSPIRA AUSTRALIA PTY  
1-23 LEXIA PLACE  
MULGRAVE NORTH, VICTORIA, AUSTRALIA

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE LABELER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER  
FINISHED DOSAGE STERILITY TESTER

**Estab. Comment:** DRUG SUBSTANCE: ACCEPTANCE TESTING  
DRUG PRODUCT (DP): EXPIENT AND COMPONENT TESTING, MANUFACTURE OF DRUG PRODUCT; IN-PROCESS CONTROL TESTING, RELEASE TESTING, STERILITY TESTING, STABILITY TESTING, PACKAGING AND LABELING FOR DRUG PRODUCT.  
APPLICATION LISTS ADDRESS AS: 1 LEXIA PLACE...  
ADDITIONAL CONTACT IS JUSTIN DALY, PHONE + 61 3 8541 5314, FAX + 61 3 8541 5081, EMAIL: JUSTIN.DALY@HOSPIRA.COM  
(on 25-JAN-2010 by D. MESMER (HFD-800) 301-796-4023)

**Profile:** STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-JAN-2010				MESMERD
SENT TO DO	28-JAN-2010	10-Day Letter			INYARDA
DO RECOMMENDATION	06-FEB-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	09-FEB-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** **CFN:** **FEI:**  
 JIANGSU HANSEN PHARMACEUTICAL CO LTD  
 (b) (4)  
 LIAN YUNGANG, JIANGSU, CHINA 222000

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
 (b) (4)

**Estab. Comment:** (b) (4)

CMC REVIEWER (JOYCE CRICH WOULD LIKE TO ATTEND THE INSPECTION.) (on 13-JAN-2010 by D. MESMER (HFD-800) 301-796-4023)

**Profile:** (b) (4)

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-JAN-2010				MESMERD
SUBMITTED TO DO	28-JAN-2010	GMP Inspection			INYARDA
DO RECOMMENDATION	06-FEB-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	09-FEB-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: FEI: (b) (4)

JIANGSU HANSEN PHARMACEUTICAL CO., LTD.

(b) (4)

LIANYUNGANG, JIANGSU, CHINA

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER (b) (4)

**Estab. Comment:** (b) (4)

(b) (4) CMC REVIEWER, JOYCE CRICH WOULD LIKE TO ATTEND THE INSPECTION. (on 13-JAN-2010 by D. MESMER (HFD-800) 301-796-4023)

**Profile:** (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-JAN-2010				MESMERD
OC RECOMMENDATION 2008 PAI COVERED GEMCITABINE - VAI	28-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)  
 (b) (4)  
 DMF No: AADA:  
 Responsibilities: (b) (4)  
 Estab. Comment: (b) (4)  
 Profile: (b) (4) (on 13-JAN-2010 by D. MESMER (HFD-800) 301-796-4023)  
 OAI Status: POTENTIAL OAI

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-JAN-2010				MESMERD
OC RECOMMENDATION	28-JAN-2010			ACCEPTABLE BASED ON PROFILE DISTRICT RECOMMENDATION	INYARDA