

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 4, 2018

To: Nataliya Fesenko PharmD, R.Ph
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on the proposed prescribing information (PI) and Instructions for Use (IFU) for INFUGEM (gemcitabine in sodium chloride injection) for intravenous use

NDA: 208313

Office of Prescription Drug Promotion (OPDP) has reviewed the proposed PI and IFU for INFUGEM (gemcitabine in sodium chloride injection) for intravenous use (INFUGEM) as requested by Division of Oncology Products (DOP2) in the consult dated May 15, 2018.

OPDP's review of the proposed PI and IFU is based on a proposed draft PI, and draft IFU send by electronic mail on June 22, 2018 to OPDP (Nazia Fatima) from DOP2 (Nataliya Fesenko). OPDP has reviewed the proposed drafts and have no comment.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAZIA FATIMA
07/04/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review: June 12, 2018

Requesting Office or Division: Division of Oncology Products 2 (DOP2)

Application Type and Number: NDA 208313

Product Name and Strength: Infugem (gemcitabine hydrochloride in 0.9% sodium chloride injection), 1,200 mg in 120 mL, 1,300 mg in 130 mL, 1,400 mg in 140 mL, 1,500 mg in 150 mL, 1,600 mg in 160 mL, 1,700 mg in 170 mL, 1,800 mg in 180 mL, 1,900 mg in 190 mL, 2,000 mg in 200 mL, 2,200 mg in 220 mL

Product Type: Single ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Sun Pharmaceutical Industries, Inc.

FDA Received Date: February 16, 2018

OSE RCM #: 2018-390

DMEPA Safety Evaluator: Colleen Little, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review responds to a DOP2 consult request for DMEPA to evaluate the proposed Infugem (NDA 208313) prescribing information (PI), container labels, carton labeling, and Instructions for Use (IFU) to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials found the proposed Infugem injection PI, container labels, carton labeling, and IFU may be improved to promote safe use of this product.

We deferred to the Office of Pharmaceutical Quality (OPQ) on the appropriateness of the (b) (4) symbol in our Human Factors Results, Label, Labeling, and Packaging Review^a on April 17, 2017. Subsequently, Sun Pharmaceuticals, Inc was issued a Complete Response on May 23, 2017 which included additional comments and recommendations that stated, "Please remove (b) (4)"^b Therefore, we provide a recommendation related to this point in section 4 below.

^a Townsend, O. Human Factors Results, Label, Labeling, and Packaging Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 17. RCM No.:2016-2719.

^b Biale, M. Complete Response for NDA 208313, gemcitabine injection. Silver Spring (MD): FDA, CDER, OND, DOP2 (US); 2017 MAY 23.

We note the use of the package type term, “single-dose (b) (4)” on container labels, overwrap labeling, and carton labeling. We also note the use of the package term type “(b) (4)” in PI and Instruction for Use (IFU). We consulted CMC during a June 7, 2018 internal meeting for the determination of the correct package type term. CMC confirmed the appropriate package type term is “single-dose bag.”

4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed PI, container labels, and carton labeling for Infugem maybe improved to promote the safe use of the product as described in Section 4.1 and 4.2.

Upon reassessing the proposed use of ‘dose-banding,’ which involves rounding the prescribing dose to a dose that can be administered using 1 or a combination of 2 bags, we again defer to the review team’s expertise on the appropriateness of the proposed use of dose banding, which as proposed, could occur without consultation with the prescriber.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

1. We defer to the Office of Pharmaceutical Quality (OPQ) on the appropriate established name. It is listed inconsistently in PI and container labels as Gemcitabine (b) (4) in Sodium Chloride Injection and as Gemcitabine (b) (4) in 0.9% Sodium Chloride Injection. Additionally, we note the May 23, 2017 CR letter additional “carton and container labeling” recommendation 4.a stated “Delete (b) (4) ‘0.9% sodium chloride’ in the established name.”

B. Prescribing Information

1. Please see Appendix H for our PI recommendations in track changes.

4.2 RECOMMENDATIONS FOR SUN PHARMECAUTIALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels, Overwrap Labeling & Carton Labeling)

1. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.^{c,d}
 - a. For the expiration date, we recommend using a format such as MMMYYYY (e.g. JAN2019) or MMMDDYYYY (e.g. JAN312019) to minimize confusion and reduce the risk for deteriorated drug medication errors.^a

^c Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^d Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

2. Revise the package type term from “single-dose (b) (4)” to “single-dose bag” on container labels and overwrap and carton labeling.

B. Container label, Overwrap and Carton Labeling

1. Remove (b) (4)

C. Container Labels

1. We note the presence of the header of the lot number and expiration date in the overprinting area of the infusion bag. We also note the presence of (b) (4) on the container label. Remove (b) (4) as the header for lot number and expiration date should be immediately next to the actual lot number and expiration date. Ensure that the lot number and expiration date are printed with headers “Lot No.” or “Lot #” and “EXP,” respectively.

D. Instructions for Use (IFU)

1. For consistency across labeling, consider replacing the statement, “Instructions for Use: Selecting the Correct (b) (4) Bag(s) with “Instructions for Use: Selecting the Correct Infugem Bag(s).”
2. For consistency across labeling, replace the statement, “INFUGEM for intravenous use is a clear, colorless, (b) (4).” with the statement, “Premixed Intravenous Solution. Do NOT remove or add medication.” which is proposed on the infusion bag label.
3. Add a cautionary statement that informs users that this product requires rounding the dose to available bag strength(s) under the heading “Understanding the Dose Ranges.”
4. To mitigate the potential for errors using the wrong table, which occurred in the human factors study, change instruction #1 under the “Selecting the Correct Bag(s)” instructions to read,
Use Table 1 for 1,000 mg/m² doses (ovarian cancer, non-small cell lung cancer, and pancreatic cancer)
Use Table 2 for 1,250 mg/m² doses (breast cancer and non-small lung cancer)
5. Retain the cautionary statements that appear under the “Selecting the Correct Bag(s)” heading (i.e., those printed in red font), but further increase their prominence (e.g., increase the font size).
6. Change the section, “Instructions for Use: Spiking the Bag” to read, “Preparation and Administration” and include instruction on how to infuse two infusion bags.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Infugem received on February 16, 2018 from Sun Pharmaceutical Industries, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Infugem and the Listed Drug		
Product Name	Infugem	Gemzar (listed drug)
Initial Approval Date	N/A	May 15, 1996
Active Ingredient	gemcitabine	gemcitabine
Indication	<p>In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.</p> <p>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p>In combination with cisplatin for the treatment of non-small cell lung cancer.</p> <p>As a single agent for the treatment of pancreatic cancer.</p>	<p>In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.</p> <p>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p>In combination with cisplatin for the treatment of non-small cell lung cancer.</p> <p>As a single agent for the treatment of pancreatic cancer.</p>
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	For Injection
Strength	1,200 mg in 120mL 1,300 mg in 130mL 1,400 mg in 140mL 1,500 mg in 150mL 1,600 mg in 160mL 1,700 mg in 170mL 1,800 mg in 180mL	200 mg and 1,000 mg

	1,900 mg in 190mL 2,000 mg in 200mL 2,200 mg in 220mL	
Dose and Frequency	<p><u>Ovarian Cancer:</u> 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Breast Cancer:</u> 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Non-Small Cell Lung Cancer:</u> 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Pancreatic Cancer:</u> 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.</p>	<p><u>Ovarian Cancer:</u> 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Breast Cancer:</u> 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Non-Small Cell Lung Cancer:</u> 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Pancreatic Cancer:</u> 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.</p>
How Supplied	single (b) (4) intravenous infusion bag.	single (b) (4) vials
Storage	25°C (77°F) (b) (4) excursions between 15° and 30°C (59° and 86°F)	Controlled room temperature 20° to 25°C (68° to 77°F) (b) (4) excursions between 15° and 30°C (59° and 86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 15, 2018, we searched DMEPA's previous reviews using the terms, "gemcitabine". Our search identified 3 previous reviews,^{e fg} and we confirmed that our previous recommendations were implemented or considered.

^e Townsend, O. Human Factors Protocol Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 27. RCM No.: 2015-1598.

^f Townsend, O. Label and Labeling Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 11. RCM No.: 2015-787.

^g Townsend, O. Human Factors Results, Label, Labeling, and Packaging Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 17. RCM No.:2016-2719.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error data, we reviewed the following Infugem labels and labeling submitted by Sun Pharmaceutical Industries, Inc. on February 16, 2018.

- Container labels
- Overwrap labeling
- Carton labeling
- Instructions for Use
- Prescribing Information (Image not shown)

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

^h Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

COLLEEN L LITTLE
06/13/2018

CHI-MING TU
06/13/2018

HUMAN FACTORS RESULTS, LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 17, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 208313
Product Name and Strength:	Infugem (Gemcitabine Hydrochloride) Injection, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharmaceutical Industries, Ltd.
Submission Date:	November 23, 2016
OSE RCM #:	2016-2719
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director (Acting):	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review documents our evaluation of the Human Factors (HF) validation study report, proposed container labels, proposed carton labeling, proposed Prescribing Information (PI) and proposed Instructions for Use (IFU) for gemcitabine hydrochloride in sodium chloride injection submitted as 505(b)(2) application under NDA 208313. The Division of Oncology Products 2 (DOP2) requested that DMEPA review the HF validation report and proposed labels and labeling from a medication error perspective as part of the evaluation of the resubmission of this application.

2 REGULATORY HISTORY

On March 30, 2015, Sun Pharmaceutical Industries, Ltd. (SPIL) submitted NDA 208313. This NDA proposes a new dosage form of gemcitabine hydrochloride. SPIL is proposing a “ready to infuse” formulation in ten presentations, which they propose will allow dosing for patients with Body Surface Areas (BSAs) ranging from 1.2 m² to 2.6 m². Gemcitabine is currently available as powder for injection and injection solution formulations that must be further diluted prior to intravenous administration.

Under pre-NDA 203652^a, a Pre-NDA meeting was held on October 31, 2014. During the meeting, the Agency expressed concerns with the number of bag strengths that would be available for user selection and the requirement that more than one bag may be needed to provide prescribed doses that are not available by using a single ready-to-infuse bag. To address the Agency’s concerns regarding the risk of selecting the wrong bag(s) resulting in an overdose or underdose, SPIL conducted a risk-assessment of the packaging and labeling, and a labeling comprehension study to determine whether users could select the appropriate product (i.e., strength) when presented with an order for gemcitabine. Based on the results of their risk assessment and labeling comprehension study, the Applicant implemented mitigation strategies to address identified risks.

In their March 30, 2015 submission, SPIL stated, “A human factor study shall be performed as recommended by (b) (4) to ensure implemented mitigation strategy as well as changes to label and IFU while prescribing, selecting, preparing and administering proposed gemcitabine product.” However, they did not include a proposed protocol in their submission nor did they indicate the status of the validation study. As a result, we submitted an Information Request on Friday, June 19, 2015 requesting that the Applicant provide the status of the validation study and encouraged them to submit the validation study protocol for our review if it had not commenced.

^a Original NDA (pNDA) submitted by Sun Pharma Advanced Research Company LTD (SPARC). When Sun Pharmaceutical Industries, Ltd. (SPIL) attempted to submit the NDA under the pre-assigned NDA number, they were told they could not because their name, SPIL, did not match the original Sponsor’s name, SPARC. Therefore, SPIL was assigned a new NDA number.

On July 13, 2015, SPIL submitted the validation study protocol for our review. Based on our evaluation of the proposed protocol and associated labeling, we provided recommendations to the Sponsor.^b

Due to deficiencies found during a facility inspection, the Agency completed the review cycle and issued a Complete Response (CR) letter to the Applicant on November 15, 2015. Our recommendations for the validation study protocol review were included in the CR letter. The validation study results were included in their November 23, 2016 resubmission, the subject of this review.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In this resubmission, the Applicant addressed our recommendations included in the CR letter. Therefore, we do not have any further concerns regarding the study protocol.

In addition, the Applicant tested the revised IFU with BSA range and dose range in the HF Validation Study.

Human Factors (HF) Validation Study Results

The HF study design included dose identification and calculation tasks for user group 1 (pharmacists and pharmacy technicians) and dose confirmation and preparation tasks for user group 2 (Oncology Registered Nurses (RN)). User group 1 participants were given a dose card

^b Townsend, O. Human Factors Protocol Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 27. RCM No.: 2015-1598.

with a calculated dose (listed in mg) and a prescribed dose level (listed in mg/m²). Based on the assigned test scenario, participants needed to identify the appropriate strength bag(s) from a total of 10 different strengths to successfully complete the task. User group 2 participants were provided with a gemcitabine bag(s) from the pharmacy and needed to identify whether the bag(s) strength matched the patient's dose, and prepare the bag(s) for administration.

There was one task failure in the study, where one pharmacy participant (pharmacy technician) failed to identify the correct bag. In this instance, the participant was presented with an 'Rx Card' containing a calculated gemcitabine dose of 1,550 mg and a prescribed dose level of 1,250 mg/m². The participant misinterpreted the dose as 1,555 mg and without referencing the IFU, rounded up to 1,600 mg. When prompted by the moderator to cross check his selection with the IFU, the participant referred to Table 1 in the IFU. Table 1 is intended to be referenced when the patient's prescribed gemcitabine dose is 1,000 mg/m². In this scenario, the user should have referred to Table 2 which should be referenced when the patient's dose is 1,250 mg/m². Within this task failure, the participant first misinterpreted the gemcitabine dose as 1,555 mg instead of 1,550 mg and then referred to the wrong table. When the moderator obtained subjective feedback, the participant stated that he did not read the IFU, but rounded the dose up to 1,600 mg based on his own knowledge and didn't realize there was a difference between the two tables in the IFU. Subsequently, the participant was able to perform the task correctly on the second and third trial. Within the report, the Applicant concluded that no changes to the IFU were required and there is no way to control whether users actually read the IFU. The Applicant also concluded that when users reference the IFU during bag selection, participants can correctly differentiate between the two tables. We have provided additional recommendations in section 5.1 below to further optimize the presentation of these two tables.

Previously, we recommended that the Applicant include tasks in their HF study to assess the effectiveness of their proposed labeling and the IFU in addressing the risk of omission of the second infusion bag when two bags are required to achieve a prescribed dose. From a medication error perspective, omission of the second bag is less harmful than infusion of an additional bag. According to the Naomi Horiba, MD (DOP2 Medical Officer), short term toxicity with overdose can lead to infection, need for transfusion and/or bleeding, while long term risk of under-treatment could lead to disease progression. However, this would be very hard to measure based on a single bag omission. To assess this risk, the Applicant included a question during the "prepare bag task" to assess whether the participants assigned to doses requiring two infusion bags would hang the second bag after completion of the first bag. The moderator asked "Let's imagine that your bag was empty. What would you do next?" All of the participants removed the first infusion bag from the IV pole and prepared the second infusion. However, we find the question may have been leading participants and may not have adequately assessed whether the proposed labeling was effective in addressing the risk of omitting the infusion of a second bag. We also noted two participants in the study stated they were unsure how to infuse the second bag (See Appendix C for more details). Because of the subjective feedback from the participants in the human factors study and our evaluation of the labeling,

we find that additional administration instructions should be included in both the IFU and PI on how to administer two gemcitabine bags. We have provided additional recommendations in section 5.1 below to include instructions pertaining to the proper administration technique required to infuse two bags and to mitigate the residual risk of omission.

Prescribing Information (PI) & Considerations in Clinical Setting

The Applicant proposed two tables (Tables 5 and 6)^c in Section 2.6 (Preparation for Intravenous Infusion Administration) of the PI that appear to be targeted for use by nurses or pharmacists who select and prepare Gemcitabine. As proposed, the user would select the appropriate bag(s) strength based on the patient's body surface area (BSA) and prescribed dose (mg/m²) based on predetermined dose banding (rounding). As stated in our previous review^b, as proposed, Table 5 and 6 in the PI appear to designate the responsibility of selecting the dose (infusion bag strength) to the pharmacist or nurse, thus excluding the prescriber from this selection decision of the final dose. This could be interpreted as the pharmacist or nurse prescribing the dose, which is prohibited by some state laws. Therefore, the proposed tables should be moved to a more appropriate location, or re-titled in a manner that guides the prescriber in which bag strengths to prescribe for the final dose versus guiding a pharmacist or nurse on what dose to dispense or administer.

Additionally, a prescriber who is prescribing Gemcitabine may not know which Gemcitabine product an institution's pharmacy stocks so a prescriber may not know which Gemcitabine PI to use for reference during prescribing. Because there are multiple approved gemcitabine products, it may be difficult for a prescriber to know if the patient's calculated dose should be banded (rounded) as required by the proposed gemcitabine product. The option of relocating Tables 5 and 6 from section 2.6 (Preparation for Intravenous Infusion Administration) to a specific dosing section intended for the prescriber immediately following the usual dosage statements (sections 2.1 to 2.5) would likely aid the prescriber in rounding the dose to an appropriate available bag strength during prescribing, but only if the prescriber references the PI for the proposed product and the product is stocked by the institution.

Product Design

This proposed product in infusion bags is beneficial in the clinical setting because it does not require manipulation by the end user. Thereby reducing the risk of exposure of the user to a cytotoxic agent, reducing the likelihood of microbial contamination during preparation, and reducing the time that a patient would spend in the infusion center waiting for drug to be prepared. On the other hand, the proposed product requires dose banding during bag selection in the proposed PI Tables 5 and 6, which as proposed, could occur without consultation with the prescriber. However, we defer to the review team's expertise on the appropriateness of the proposed use of dose banding, which as proposed, could occur without consultation with the prescriber.

^c Table 5 is intended to be used for the selection of gemcitabine infusion bags for patients being treated with a dose level of 1,000 mg/m² and Table 6 is intended for patients being treated with a dose level of 1,250 mg/m²

5 CONCLUSION & RECOMMENDATIONS

The HF study results indicated that the tables provided in the instructions for use (IFU) could be used incorrectly for a given prescribed dose. In addition, there is residual risk of omission of a second infusion bag, when required. However, our concerns can be addressed further with labeling.

We also find the proposed container labels and carton labeling acceptable, but we deferred to the Office of Pharmaceutical Quality (OPQ) on the appropriateness of the (b) (4) symbol. They have determined the symbol is ambiguous and they plan to recommend that it be removed.

If the review team determines that the proposed dose banding is appropriate for the proposed Gemcitabine Injection in Sodium Chloride, we have the following recommendations to promote the safe use of the product.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Add a cautionary statement at the beginning of Section 2 (Dosage and Administration) that informs prescribers that this product requires rounding the dose to available bag strength(s).
2. Create a new subsection in Section 2 that instructs the prescriber how to round the prescribed dose to available bag strength(s). Include the paragraph currently in section 2.6 that reads “Recommended doses of gemcitabine...BSA based calculated dose by no more than 5%.” in this new subsection.
 - a. This subsection should immediately follow the usual dosage statements (sections 2.1 to 2.5).
 - b. This subsection could be titled, “Infusion Bag Selection Based on Patient’s Body Surface (BSA)”.
 - c. Relocate Tables 5 and 6 to immediately follow the introductory statements in this new subsection.
3. Change the title of subsection 2.7 from (b) (4) to “Administration” and based on data from the Applicant, include instructions for the user on how to appropriately administer two gemcitabine bags. This should include the administration sequence (e.g., simultaneous administration) and infusion rate (e.g., 30 minutes).
4. Include a statement in subsection 2.7 that reads “Based on the calculated dose, one or two gemcitabine bags may be needed.”

B. Instructions for Use (IFU)

1. For consistency across labeling, replace the statement, “TRADENAME for intravenous use is a clear, colorless, ...do not allow contamination.” with the statement, “Premixed Intravenous Solution. Do NOT remove or add medication.” which is proposed on the infusion bag label.

2. Add a cautionary statement that informs users that this product requires rounding the dose to available bag strength(s) under the heading “Understanding the Dose Ranges”.
3. To mitigate the potential for errors using the wrong table, which occurred in the human factors study, change instruction #1 under the “Selecting the Correct Bag(s)” instructions to read,
Use Table 1 for 1,000 mg/m² doses (ovarian cancer, non-small cell lung cancer, and pancreatic cancer)
Use Table 2 for 1,250 mg/m² doses (breast cancer and non-small lung cancer)
4. Retain the cautionary statements that appear under the “Selecting the Correct Bag(s)” heading (i.e., those printed in red font), but further increase their prominence (e.g., increase the font size).
5. Change the section, “Instructions for Use: Spiking the Bag” to read, “Preparation and Administration” and include instruction on how to infuse two infusion bags (see recommendation A.3 above).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gemcitabine Hydrochloride in Sodium Chloride Injection that SPIL submitted on November 23, 2016.

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug		
Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
Initial Approval Date	N/A	May 15, 1996
Active Ingredient	Gemcitabine (b) (4)	Gemcitabine
Indication	Same as Listed Drug	<p>In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.</p> <p>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p>In combination with cisplatin for the treatment of non-small cell lung cancer.</p> <p>As a single agent for the treatment of pancreatic cancer.</p>
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug

Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
Strength	1,200 mg in 120mL 1,300 mg in 130mL 1,400 mg in 140mL 1,500 mg in 150mL 1,600 mg in 160mL 1,700 mg in 170mL 1,800 mg in 180mL 1,900 mg in 190mL 2,000 mg in 200mL 2,200 mg in 220mL	200 mg and 1,000 mg
Dose and Frequency	Same as listed drug	<p><u>Ovarian Cancer:</u> 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Breast Cancer:</u> 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Non-Small Cell Lung Cancer:</u> 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Pancreatic Cancer:</u> 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.</p>

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug		
Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
How Supplied	Single-dose (b) (4) bag with an aluminum overwrap (b) (4).	200 mg lyophilized powder (b) (4) sterile single (b) (4) vial 1 g lyophilized powder (b) (4) (b) (4) sterile single- (b) (4) vial
Storage	25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Controlled room temperature 20° to 25°C (68° to 77°F) (b) (4) excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 17, 2017, we searched the L:drive and AIMS using the term, “gemcitabine” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews^{d,e} and we confirmed that our previous recommendations were implemented or considered.

^d Townsend, O. Human Factors Protocol Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 27. RCM No.: 2015-1598.

^e Townsend, O. Label and Labeling Review for Gemcitabine Hydrochloride in Sodium Chloride (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 11. RCM No.: 2015-787.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Study Objectives

Determine whether the labeling approach and associated instructional material (IFU) enable intended users (Pharmacy users and Oncology RNs) to correctly and safely fill chemotherapy prescriptions (identifying correct dose, selecting correct bag) or prepare chemotherapy infusions (confirming correct bag, preparing bag).

Assess the Pharmacy users' ability to identify and select the correct carton linked to the prescribed dose based on the labeling on the carton and the Gemcitabine dose table in the IFU.

Assess Oncology RNs ability to verify the correct dose based on the labeling of the overwrap or bag itself and to perform the bag preparation procedure based on the IFU.

Determine if specific aspects of the label and/or IFU lead to any patterns of high risk use errors when used by the intended user populations. Successful validation is demonstrated by the absence of any pattern of preventable use failure or difficulties with the procedure that could result in patient harm.

User Groups

The Human Factors Validation Study consisted of two user groups. User group 1 consisted of pharmacy users (pharmacists and pharmacy technicians) and user group 2 consisted of Oncology Registered Nurses (RN). There were 15 participants in each group.

Study Design Summary Table

	Pharmacists and Pharmacy Technicians	Oncology RNs
Number of Participants	N=15	N=15
Identification Task	Yes (2 ID tasks: different dose ranges)	No
Calculate Dose Task	Yes (2 tasks: 1 with single bag, 1 with double bag)	No
Confirmation Task (Incorrect Bag)	No	Yes
Confirmation Task (Correct Bag)	No	Yes
Prepare Bag(s) Task	No	Yes 7/15 using 1 bag 8/15 using 2 bags 7/15 with overwrap 8/15 without overwrap
Labeling Review	Yes	Yes
IFU Review	Yes	Yes

Tasks

The Critical Tasks were as follows:

- Pharmacy Identification Task #1 - Pull dose, In Carton
- Pharmacy Identification Task #2 - Calculate & Pull Dose, In Carton
- Pharmacy Identification Task #3 - Pull Dose, In Wrap
- Pharmacy Identification Task #4 - Calculate & Pull Dose, In Overwrap
- Nursing Confirmation Task #1 - Incorrect Dose
- Nursing Confirmation Task #2 - Correct Dose
- Nursing Bag Preparation Tasks
 - Remove bag from overwrap
 - Remove Cap
 - Spike Bag
 - Spike Bag with port side up
 - Spike bag while hanging on IV Pole

Use-Related Risk Analysis

Risk Level Descriptions

Risk Severity	Use Error and Potential Clinical Impact
High	All tasks that fall into a non-acceptable area that would result in serious injury or harm to a patient, or where the user would not be aware of their error, are categorized as High.
Medium	All tasks that would prevent/delay a user from dosing but a user would be aware of the failure are Medium.
Low	All tasks that are tangential to the device interaction, or not related specifically to dosing, are categorized as Low.

Summary of Potential Use Errors

Task/Item	Potential Use Error	Outcome of Use Error (Clinical Impact)	Risk Level	Bag Labeling Mitigation	IFU Mitigation
<p align="center">Identify Infusion Bag(s) for Prescription</p>	<p>Selects wrong Gemcitabine dose other than recommended in IFU.</p>	<p>Underdose or overdose.</p>	<p align="center">High</p>	<p align="center">N/A</p>	<p>IFU includes instructions and 2 tables to support selecting correct Gemcitabine dose.</p> <p>Included important warning messages to educate users on how to use the tables to determine the correct Gemcitabine bag(s).</p> <p>All dosage strengths are presented in the IFU. For each strength, the IFU includes the BSA, calculated dose range and the TRADENAME Gemcitabine infusion bag(s) required. In addition, an image of dosage strength and its</p>
	<p>Selects/confirms lower dose other than recommended in IFU.</p>	<p>Underdose.</p>			
	<p>Selects/confirms higher dose other than recommended in IFU.</p>	<p>Overdose.</p>			

Task/Item	Potential Use Error	Outcome of Use Error (Clinical Impact)	Risk Level	Bag Labeling Mitigation	IFU Mitigation
					associated color for what the user sees on the carton/overwrap.
Select/Confirm Correct Infusion Bag(s)	Selects/confirms lower dose other than recommended in IFU.	Underdose.	High	Overwrap and carton are color-coded for each dosage strength and presented in a large font size.	The PDP is printed in color in the IFU to allow the user to match the correct dosage strength to what the user will pull from the shelf.
	Selects/confirms higher dose other than recommended in IFU.	Overdose.			
Product Not for Doses Less than 1,150 mg/m²	States product can be used for calculated doses less than 1,150 mg/m ² .	Overdose.	High		Dedicated important warning statement in IFU that product cannot be used for doses less than 1,150 mg.
Remove Infusion Bag from Packaging	Does not open carton.	Delay of therapy.	Medium	N/A	N/A
	Unable to open carton.				
	Does not open overwrap.	Delay of therapy.			
	Unable to open overwrap.				
	Does not remove infusion bag from overwrap.	Delay of therapy.			
	Unable to remove infusion bag from overwrap.	Delay of therapy.			
	Uses bag where overwrap has been removed, opened or damaged.	Potential contamination.	High		Dedicated statement to not use bags that have overwrap removed, opened or damaged.
	Uses bag that has been damaged, discolored, or has	Potential contamination.	High		Dedicated statement to not use bag if

Task/Item	Potential Use Error	Outcome of Use Error (Clinical Impact)	Risk Level	Bag Labeling Mitigation	IFU Mitigation
	particulate matter.				damaged, discolored or contains particulate matter.
Break Cap	Does not break cap.	No therapy delivered.	Medium	N/A	Dedicated statement and illustrations to explain how to break tamper evident cap on infusion port.
	Unable to break cap.				
Spike Infusion Set	Does not spike bag.	No therapy delivered.	Medium	N/A	Dedicated statement and illustrations on how to spike infusion bag with infusion set.
	Unable to spike bag.		Medium		
	Does not remove spike cover (leaves spike cover on).		Medium		
	Spikes bag with port facing down.	May result in leak and exposure risk if the spike is not properly inserted.	High		
	Spikes bag while hanging on IV pole.	May result in leak and exposure risk if the spike is not properly inserted.	High		

Test Articles

- Cartons of each dosage strength
- Overwraps for each dosage strength
- Infusion bags for each dosage strength
- Instructions for Use
- IV Stands
- IV Sets
- Gloves

C.2 Results

In the pharmacy participant group, 100% of the participants successfully completed the “Rx Identification Task” and 93% (14/15) of the participants successfully completed the “Calculated Rx Task”. In the nursing participant group, 100% of the participants successfully completed all assigned tasks (confirmation and preparation).

9.1a Performance Measures – Rx Identification Tasks

	Risk Level	Rx Identification Task #1 (N=15)	Rx Identification Task #3 (N=15)	Overall (N=30)
Failure to match Gemcitabine Prescription with correct drug label/bag	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
<i>Refers to IFU</i>	N/A	0/15 (0%)	2/15 (13%)	2/30 (7%)

9.1b Performance Measures – Calculated Rx Tasks

	Risk Level	Rx Calculation Task #2 (N=15)	Rx Calculation Task #4 (N=15)	Overall (N=30)
Failure to identify the correct infusion bag based on the Gemcitabine dose	High	1/15 (7%)	0/15 (0%)	1/30 (3%)
<i>Uses correct table in IFU</i>	N/A	14/15 (93%)	15/15 (100%)	29/30 (97%)
Failure to match Gemcitabine prescription with correct drug label/bag	High	0/15 (0%)*	0/15 (0%)	0/30 (0%)

*Note: Even P9, who misread the calculated dose, correctly matched his 1,600 mg Gemcitabine prescription with the correct drug label/bag. Respectively, P9 correctly pulled the drug label/bag that he intended to pull, which demonstrates that the labeling approach is successful in communicating the dose amount.

9.5a Subjective Measures – IFU Review

Q: Overall, did you have any difficulty understanding the instructions?

	Pharmacy Users (N=15)	RNs (N=15)	Overall (N=30)
Yes	0/15 (0%)	0/15 (0%)	0/30 (0%)
No	15/15 (100%)	15/15 (100%)	30/30 (100%)

Pharmacy User Comments:

- P1- No. Using the table in the instructions makes it a lot easier because I don't have to use my own memory to calculate the dosage. This is really easy with the breakdown.

RN Comments:

- P21- No. The instructions are pretty clear. I like the pictures and the step by step instructions.
- P22- No. I was looking for information on whether you should use the larger bag or the smaller bag first, if you're using two bags.

Q: Overall, did you have any difficulty knowing which table to reference for the patient's Gemcitabine dose and prescribed dose?

	Pharmacy Users (N=15)	RNs (N=15)	Overall (N=30)
Yes	0/15 (0%)	0/15 (0%)	0/30 (0%)
No	15/15 (100%)	15/15 (100%)	30/30 (100%)

Pharmacy User Comments:

- P9- No. In the beginning I did, but not anymore. After reading the instructions, I understand.

RN Comments:

- P21- No. It's good that all the doses are different colors.
- P22- No. But the headers for each table are a little confusing. It was easier for me to first look at the content of the tables rather than the dose strength. Now it is clear.

Q: Overall, did you find the content readable in terms of font size, type and overall format?

	Pharmacy Users (N=15)	RNs (N=15)	Overall (N=30)
Yes	15/15 (100%)	15/15 (100%)	30/30 (100%)
No	0/15 (0%)	0/15 (0%)	0/30 (0%)

Pharmacy User Comments:

- P3- Yes. But the numbers in the tables under the calculated dose column are a little difficult to read because it's so scrunched. Maybe if they could round the numbers. If that's not possible, it would be better to increase the number size about 50% bigger. This would just be an enhancement. If the text size stayed where it is, I wouldn't have any problem reading it.

Q: Are there any changes to the instructions that you feel are needed to prevent any confusion or difficulties you experienced today?

	Pharmacy Users (N=15)	RNs (N=15)	Overall (N=30)
Yes	0/15 (0%)	0/15 (0%)	0/30 (0%)
No	15/15 (100%)	15/15 (100%)	30/30 (100%)

Pharmacy User Comments:

- *P1- No. I wish more of the drugs were like this. This is really great!*
- *P2- No. The instructions are really clear and good.*
- *P3- No. When there are two bags, do you give them at the same time or one first and then the other? Usually, Gemcitabine is given over 30 minutes. So some indication of this would be helpful to know.*
- *P4- No. I wasn't paying much attention to the calculated dose column in the tables. But there's nothing that could change to draw my attention to it.*
- *P4- No. It's very easy to identify doses because of the colors.*
- *P9- No. I think it's self-explanatory.*
- *P13- No. But I think the IFU should indicate that the infusion set does not come with the product.*

RN Comments:

- *P17- No. I think the instructions are really good. I like the pictures.*
- *P20- No. I think it's well labeled and it is certainly as useful for the pharmacist, also.*
- *P21- No. I think it's good that it's all colored differently and it stands out.*
- *P27- No. The color-coding really helps!*
- *P28- No. The instructions are pretty clear.*

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Gemcitabine Hydrochloride Injection labels and labeling submitted by Sun Pharmaceutical Industries, Ltd. on November 23, 2016.

- Container labels
- Carton labeling
- Instructions for Use
- Prescribing Information

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

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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OTTO L TOWNSEND
04/17/2017

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04/18/2017

QUYNHNHU T NGUYEN
04/18/2017

DANIELLE M HARRIS
04/18/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information**

Memorandum

Date: 09/06/16

To: Mimi Biable
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Gemcitabine Hydrochloride
NDA 208313

Office of Prescription Drug Promotion Comments on proposed package insert (PI), Carton/Container Labeling and Instructions for Use (IFU)

Office of Prescription Drug Promotion (OPDP) acknowledges the receipt of the April 4, 2015, consult request from DOP2 for labeling review of the proposed PI, Carton/Container Labeling and IFU.

DOP2 plans to issue a Complete Response (CR) letter. Therefore, OPDP defers comment on the Applicant's PI, PPI and Carton/Container Labeling at this time. A final review will be performed after the CR letter.

OPDP requests that DOP2 submit a new consult request during a subsequent review cycle to provide comments regarding labeling for this application.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
09/06/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 11, 2015

Requesting Office or Division: Division of Oncology Product 2 (DOP2)

Application Type and Number: NDA 208313

Product Name and Strength: Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection,
10 mg/mL

Product Type: Single Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Sun Pharmaceutical Industries, Ltd. (SPIL)

Submission Date: March 30, 2015

OSE RCM #: 2015-787

DMEPA Primary Reviewer: Otto L. Townsend, PharmD

DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

On March 30, 2015, Sun Pharmaceutical Industries, Ltd. (SPIL) submitted NDA 208313. This NDA proposes a new dosage form of gemcitabine hydrochloride. SPIL is proposing a “ready to infuse” formulation in ten presentations, which they propose will allow dosing for patients with Body Surface Areas (BSAs) ranging from 1.2 m² to 2.6 m².

In the Pre-NDA meeting held on October 31, 2014, FDA expressed concerns with the number of bag strengths that would be available for user selection and the use of more than one bag to provide a prescribed dose. To address concerns with appropriate bag selection to prevent overdose or underdose, SPIL conducted a risk-assessment of the packaging and labeling, and plans to complete human factors testing to validate that users can select the appropriate product (i.e., strength) when presented with an order for gemcitabine. However, there does not appear to be any proposal from SPIL to address the use of more than one bag to provide a prescribed dose at the time of this review.

The Division of Oncology Products 2 (DOP2) requested that we review the proposed container labels, overwrap and carton labeling, Prescribing Information and other labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

If approved, this Application would introduce the first “ready-to-infuse” gemcitabine hydrochloride intravenous infusion bag. The product would be available in a concentration of 10 mg/mL and would be available in 10 strengths (see Appendix A). During the pre-NDA meeting, the Agency expressed concerns that proposed container labels, overwrap and carton labeling may not adequately address the risk of bag confusion during selection by the end user. To address these concerns expressed by the Agency, SPIL conducted a risk-assessment of the packaging, container labels, overwrap and carton labeling. The container labels, overwrap and carton labeling submitted on March 30, 2015 were an improvement compared to those proposed during the pre-NDA meeting.

SPIL also proposes the use of ‘dose-banding’, which involves rounding the prescribed dose to a dose that can be administered using one or a combination of two of the 10 available bag strengths. For example, a calculated dose of 1,705 mg would be rounded to the available strength of 1,700 mg for administration with the 1,700 mg strength bag. The review division has not determined whether the practice of dose-banding is acceptable for this product at the time of this review.

In addition, SPIL intends for the pharmacist or nurse to perform the dose-banding, however, neither the proposed Prescribing Information (PI) nor the Instructions for Use (IFU) inform the prescriber that the pharmacist or nurse will band (round) the prescribed dose to a dose that can be provided by the available bag strengths. The practice of dose-banding by the pharmacist or nurse could be interpreted as prescribing by the pharmacist or nurse, which is prohibited or limited in many states. Furthermore, the practice of administering two ready to infuse bags to provide the prescribed dose is error-prone. The nurse may forget or not be aware a second bag is required and omit infusion of the second bag (underdose). SPIL has not proposed any strategies to mitigate such risk of omission nor proposed to evaluate this risk in their proposed Human Factors Study at this time. Thus, we consider limiting the use of this proposed drug product to only when the prescribed dose after dose-banding will require one “ready to infuse” bag.

The newly proposed IFU lacks sufficient details and instructions for the user. As an example, the only instruction for the user is to, (b) (4)

(b) (4) Along with a cautionary statement that the product is not intended for patients with Body Surface Areas not listed in the IFU. In addition, the tables are not clearly labeled and differentiated to help the end users understand which table should be used under different circumstances. (b) (4)

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

The container labels, overwrap and carton labeling, and PI can be further improved to promote safe use of the product. Please note that our recommendations for Instructions for Use (IFU) were already provided in a separate Human Factors review¹ in DARRTS (See DARRTS NDA 208313 Human Factors Review dated 8/27/2015).

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

1. Our recommendations are based on the assumption that DOP2 will find the concept of dose-banding acceptable for this Application. The details of how this will be performed would need to be determined.
2. We defer to the Office of Pharmaceutical Quality (OPQ) on the appropriate product name. It is listed inconsistently in PI and container labels as Gemcitabine (b) (4) in Sodium Chloride Injection and as Gemcitabine (b) (4) in 0.9% Sodium Chloride Injection. Furthermore, we defer to OPQ on whether the abbreviation, (b) (4) should follow the words, "Sodium Chloride Injection".
3. Based on the currently proposed PI, the prescriber would not be aware that dose-banding would be performed by the pharmacist or nurse. SPIL intends for the pharmacist or nurse would round the prescribed dose to a dose that can be

¹ Townsend, O. Human Factors Protocol Review for Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 27. RCM No.: 2015-1598.

administered using one or a combination of two of the 10 available bag strengths. This rounding of dose without notifying the prescriber would equate to prescribing by the nurse or pharmacist, which state laws prohibit or limit in most states.

4. Patients with BSAs ranging from 1.2 m² to 2.6 m² and who require a dose that cannot be provided by only one infusion bag will require the administration of two bags. We find this practice error prone as the second bag may be omitted or an additional bag may be administered. This could result in an overdose or an underdose. We recommend that this product only be used for patients where the prescribed dose (whether calculated or banded by the prescriber) is provided by the infusion of one bag. For example: If the prescribed dose requires the administration of more than one ready to infuse bag, the dose should be prepared extemporaneously by the facility from other Gemcitabine HCl products (e.g. Gemcitabine Injection supplied in vials).

B. Prescribing Information

1. If the practice of dose-banding is found acceptable for this product, we recommend that more details be provided in the Dosage and Administration section to help guide the prescriber in determining the appropriate banded dose of Gemcitabine. Dose-banding should be performed by the prescriber instead of the pharmacist or nurse (See Comment A3 above).
2. If the Review Team determines the infusion of two bags is acceptable, we recommend addition of administration instructions to remind healthcare professionals that both bags must be infused to provide the full dose.

C. Container Labels and Carton Labeling

1. We defer to OPQ on the appropriateness of the (b) (4) symbol.

(b) (4)

4.2 RECOMMENDATIONS FOR SPIL

We recommend the following be implemented prior to approval of this NDA:

1. Assigning National Drug Codes (NDC) (b) (4)
(b) (4)
(b) (4)
(b) (4) To better differentiate National Drug Codes, thus differentiate

the different strengths, we recommend changing the product codes (b) (4)

[Redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gemcitabine Hydrochloride in Sodium Chloride Injection that SPIL submitted on March 30, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug		
Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
Initial Approval Date	N/A	May 15, 1996
Active Ingredient	Gemcitabine (b) (4)	Gemcitabine
Indication	Same as Listed Drug	<p>In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.</p> <p>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p>In combination with cisplatin for the treatment of non-small cell lung cancer.</p> <p>As a single agent for the treatment of pancreatic cancer.</p>
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug		
Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
Strength	1,200 mg in 120mL 1,300 mg in 130mL 1,400 mg in 140mL 1,500 mg in 150mL 1,600 mg in 160mL 1,700 mg in 170mL 1,800 mg in 180mL 1,900 mg in 190mL 2,000 mg in 200mL 2,200 mg in 220mL	200 mg and 1,000 mg
Dose and Frequency	Same as listed drug	<u>Ovarian Cancer:</u> 1000 mg/m ² over 30 minutes on Days 1 and 8 of each 21-day cycle. <u>Breast Cancer:</u> 1250 mg/m ² over 30 minutes on Days 1 and 8 of each 21-day cycle. <u>Non-Small Cell Lung Cancer:</u> 1000 mg/m ² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m ² over 30 minutes on Days 1 and 8 of each 21-day cycle. <u>Pancreatic Cancer:</u> 1000 mg/m ² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug

Product Name	Gemcitabine ^{(b) (4)} in Sodium Chloride	Gemzar
How Supplied	One single-dose ^{(b) (4)} bag with an aluminum overwrap ^{(b) (4)} .	200 mg lyophilized powder ^{(b) (4)} sterile single ^{(b) (4)} vial 1 g lyophilized powder ^{(b) (4)} sterile single- ^{(b) (4)} vial
Storage	25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Controlled room temperature 20° to 25°C (68° to 77°F) ^{(b) (4)} excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 29, 2015, we searched the L:drive and AIMS using the term, 'gemcitabine' to identify reviews previously performed by DMEPA.

B.2 Results

Since this is the first gemcitabine "ready-to-infuse" product, our previous labeling reviews did not contain recommendations that were applicable to this review. In conjunction with this Label and Labeling Review, we also completed a Human Factors Protocol Review².

² Townsend, O. Human Factors Protocol Review for Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection (NDA 208313). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 27. RCM No.: 2015-1598.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 29, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Gemcitabine

D.2 Results

Our search did not yield any reports that described medication errors or actions possibly associated with the label and labeling of currently marketed gemcitabine products.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Gemcitabine Hydrochloride in Sodium Chloride Injection labels and labeling submitted by SPIL on March 30, 2015.

- Container labels
- Overwrap labeling
- Carton labeling
- Instructions for Use
- Prescribing Information

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

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review: August 27, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 208313
Product Name and Strength: Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Sun Pharmaceutical Industries, Ltd. (SPIL)
Submission Date: July 13, 2015
OSE RCM #: 2015-1598
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD
Associate Director: Lubna Merchant, PharmD

1 REASON FOR REVIEW

On March 30, 2015, Sun Pharmaceutical Industries, Ltd. (SPIL) submitted NDA 208313. This NDA proposes a new dosage form of gemcitabine hydrochloride. SPIL is proposing a “ready to infuse” formulation in ten presentations, which they propose will allow dosing for patients with Body Surface Areas (BSAs) ranging from 1.2 m² to 2.6 m².

In the Pre-NDA meeting held on October 31, 2014, FDA expressed concerns with the number of bag strengths that would be available for user selection and the use of more than one bag to provide a prescribed dose. To address concerns with appropriate bag selection to prevent overdose or underdose, SPIL conducted a risk-assessment of the packaging and labeling, and human factors testing to validate that users can select the appropriate product (i.e., strength) when presented with an order for gemcitabine.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

If approved, this Application would introduce the first “ready-to-infuse” gemcitabine hydrochloride intravenous infusion bag. The product would be available in a concentration of 10 mg/mL and would be available in 10 strengths (see Appendix A). SPIL has submitted a Human Factors (HF) protocol for review prior to commencing the study.

SPIL included an Instruction for Use (IFU) document in the submission of the proposed protocol. The proposed Prescribing Information (PI) submitted with the NDA does not reference the IFU nor does the IFU refer the reader to the PI. The IFU lacks sufficient details and instructions for the user. As an example, the only instruction for the user is to, (b) (4)

with a cautionary statement that the product is not intended for patients with BSAs not listed in the IFU. In addition, the tables are not clearly labeled and differentiated so that the user understands which table should be used and under which circumstances.

Neither the proposed PI nor the IFU inform the prescriber that the pharmacist or nurse will band (round) the prescribed dose to a dose that can be provided by one of the available bag strengths. This could be interpreted as prescribing by the pharmacist or nurse, which is prohibited or limited in many states. In addition, the review division has not determined whether the practice of dose banding is acceptable for this product at the time of this review.

The IFU lists BSA, but there is no task listed in the protocol to assess end users' understanding of this information and how end users will use this information to determine the dose, perform dose banding, and finally select the bags of Gemcitabine HCl in 0.9% Sodium Chloride Injection. According to the protocol, the prescription card will contain a dose, but not the BSA. In addition, the IFU does not provide clear instruction on how to round the dose based on BSA or prescribed dose. For example, in a patient who has a BSA of 1.75 m² and requires a dose of 1,000 mg/m², the calculated dose is 1,750 mg. Which available bag strength would the user or prescriber select, 1,700 mg or 1,800 mg? A dose of '1,700' is listed in Appendix B (Condition Log), but the dose that will be printed on the prescription card is not indicated in the protocol.

According to the proposed HF protocol, the participants will be provided with an IFU and asked to review it at the beginning of the identification task. Next, the participants will be provided with a prescription card. This does not simulate a real life scenario. Under normal circumstances, the user (pharmacist or nurse) receives a prescription first. If the user needs help with interpretation of the prescription, calculation of dose, or has other questions about the drug product, he or she would refer to the PI and/or IFU. Routinely, the PI and IFU are packaged with the drug product. The user (pharmacist or nurse) would not be aware that she needs the IFU prior to receiving the prescription.

Finally, the proposed protocol does not validate the effectiveness of the proposed labeling and IFU on ensuring nurses will complete the infusion of more than one bag for patients whose prescribed dose would require the administration of two bags.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the summative human factors protocol identified areas that require revision to ensure that the study adequately assesses the safe and effective use of the proposed product by the intended population. We recommend the protocol be revised prior to commencing the study. We provide recommendations to be conveyed to the Sponsor before they begin their summative human factor study in section 4.1 below.

4.1 RECOMMENDATIONS FOR SUN PHARMACEUTICAL INDUSTRIES, LTD

We recommend the following be implemented prior to commencing the Gemcitabine Hydrochloride in Sodium Chloride Injection summative human factors study for NDA 208313.

A. General Comments

The following recommendations focus on the proposed Human Factors protocol. Additionally, your proposed labeling plan does not reflect current healthcare practice and thus is error prone. If the practice of dose banding is found acceptable for this application, you should consider incorporating a table in the Dosage and Administration section of the Prescribing Information that instructs the prescriber to round the dose. As currently proposed, the prescriber would not be aware that the pharmacist or nurse could potentially round the prescribed dose to available bag strength. This rounding of dose without notifying the prescriber would equate to prescribing by the nurse or pharmacist, which state laws prohibit or limits in most states.

B. Human Factors Protocol & Instruction for Use (IFU)

1. Review the protocol for inconsistencies. For example, error debrief is listed in the test script, but not in the testing procedure description.
2. Clarify the intended end user for the proposed IFU. If the IFU is meant for nurses and pharmacists, then it is unclear why BSA and Target Dose are provided in the IFU when nurses and pharmacists are not permitted by state laws to round or change the prescribed dose (See related General Comments). Revise the IFU, (b) (4)
[REDACTED]
3. It appears the proposed product is intended for patients with BSAs ranging from 1.2 m² to 2.6 m²; however, the IFU contains the statement (b) (4)
[REDACTED]
[REDACTED] Clarify whether the proposed product is intended for use with patients with BSAs ranging from 1.2 m² to 2.6 m², or if it is only intended for use with the specific BSAs listed in the IFU table (e.g. 1.2 m², 1.3 m², 1.4 m², etc.).
 - a. If it's intended for the range of BSAs from 1.2 m² to 2.6 m², then provide prescribing instructions on dose banding and clarification on how dose banding should be performed for BSA values with two decimal places. For example, if a patient has a BSA of 1.75 m² and requires a dose of 1,000 mg/m² (calculated dose is 1,750 mg), then is the correct dose after dose banding 1700 mg, or 1800 mg?
 - b. If it's intended for the specific BSAs listed in the IFU table, then evaluate the effectiveness of the statement (b) (4) in the HF protocol to

provide assurance that nurses and pharmacists will not use the proposed product for a patient with BSA of 1.75 m².

4. To better simulate a real life scenario in the identification and differentiation tasks, the IFU may be provided to the participants, but do not instruct the participant to review the IFU prior to receiving the prescription card. In the usual clinical setting, the user (pharmacist or nurse) would receive a prescription first. If the user needs help with interpretation or calculation of dose, he or she would have the option to refer to the PI and/or IFU that are packaged with the drug.
5. Nurses will be required to administer two bags in some cases. We recommend inclusion of tasks that would assess how effective product labeling and the IFU are in addressing the risk of omission of the second bag to be infused by the nurse.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gemcitabine Hydrochloride in Sodium Chloride Injection that SPIL submitted on March 30, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Gemcitabine Hydrochloride in Sodium Chloride Injection and the Listed Drug		
Product Name	Gemcitabine (b) (4) in Sodium Chloride	Gemzar
Initial Approval Date	N/A	May 15, 1996
Active Ingredient	Gemcitabine (b) (4)	Gemcitabine
Indication	Same as Listed Drug	<p>In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.</p> <p>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p>In combination with cisplatin for the treatment of non-small cell lung cancer.</p> <p>As a single agent for the treatment of pancreatic cancer.</p>
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	1,200 mg in 120mL 1,300 mg in 130mL 1,400 mg in 140mL 1,500 mg in 150mL 1,600 mg in 160mL 1,700 mg in 170mL 1,800 mg in 180mL	200 mg and 1,000 mg

	1,900 mg in 190mL 2,000 mg in 200mL 2,200 mg in 220mL	
Dose and Frequency	Same as listed drug	<p><u>Ovarian Cancer</u>: 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Breast Cancer</u>: 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Non-Small Cell Lung Cancer</u>: 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.</p> <p><u>Pancreatic Cancer</u>: 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.</p>
How Supplied	One single-dose (b) (4) bag with an aluminum overwrap (b) (4).	<p>200 mg lyophilized powder (b) (4) sterile single (b) (4) vial</p> <p>1 g lyophilized powder (b) (4) sterile single (b) (4) vial</p>
Storage	25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Controlled room temperature 20° to 25°C (68° to 77°F) (b) (4) excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Study Objectives

1. Validate whether the label and associated instructional material (IFU) can be correctly, safely, and effectively used by the intended user populations (Pharmacists, Pharmacy Technicians, and Oncology Nurses).
2. Determine if specific aspects of the label and/or IFU lead to any patterns of high risk use errors when used by the intended user populations.

Study Design

The Summative Human Factors Validation Study will contain two user groups. User group 1 will consist of pharmacy users (pharmacists and pharmacy technicians) and user group 2 will consist of Oncology Registered Nurses (RN). There will be 15 participants in each group. Tasks with a risk severity level of High (a task that would result in serious injury or harm to a patient) are considered critical tasks and include:

- Identify needed infusion bag
- Select correct infusion bag from shelf
- Confirm infusion bags are correct for prescription

In order to identify how usable the labels and instructional materials are, the proposed study plans to have users perform multiple tasks that mimic real life situations that may be encountered if preparing and administering chemotherapy using the proposed infusion bags. Both user groups will complete identification and differentiation task. Only the nursing user group will complete additional confirmation tasks.

Identification Tasks

The users will be provided with an IFU and asked to review it. Next, they will be provided with a prescription card that simulates a prescription for gemcitabine. Then, asked to name bags required to fill the given prescription. The moderator will ask if they had any difficulty. If any errors are noted, the moderator will discuss with the participant and determine a cause. Three identification tasks will be completed with the following conditions:

- Identification Task 1 - prescribed dose that represents an available bag strength
- Identification Task 2 - prescribed dose that represents rounding the dose to an available bag strength
- Identification Task 3 – prescribed dose that represents combination of two available bag strengths

Differentiation Tasks

Using the IFU and prescription card provided for the tasks above, the participant will be asked to select the appropriate bag(s) from a shelf containing all the available infusion bag strengths.

Then, asked to select appropriate bags required to fill the given prescription and place the bag(s) on a table. The moderator will ask if they had any difficulty. If any errors are noted, the moderator will discuss with the participant and determine a cause.

Confirmation Tasks

In addition to the identification and differentiation tasks, the nursing user group will be asked to complete two confirmation tasks. These tasks are intended to further evaluate the effectiveness of the labeling and IFU in realistic use scenarios. The first confirmation task is intended to simulate the nursing task of confirming if a given set of infusion bags are correct or incorrect for a given prescription. The task will be performed three times, each with a different prescription. One of the three tasks will include an incorrect set of infusion bags. The second task will be performed once and is to evaluate the readability of the infusion bag label on a used bag hanging on an IV pole. The nurse will be asked to identify the dose that the bag contained when it was full.

After completion of tasks, the participant will review the IFU and asked subjective questions regarding understanding the IFU, its clarity, and readability.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Gemcitabine Hydrochloride in Sodium Chloride Injection labels and labeling submitted by SPIL on July 13, 2015.

- Instructions for Use



Gemcitabine_HF_draft
-ifu 13JUL15.doc

- Human Factors Study Protocol



Gemcitabine_human-f
ac-stdy-pro 13JUL15.p

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

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