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RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 15, 2018
From	Nina Ni, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208313-ORIG-1-RESUB-23
Type of Application	505(b)(2) – complete response resubmission
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Date of Receipt	February 16, 2018
PDUFA Goal Date	August 16, 2018 (early action date: July 20, 2018)
Proposed Proprietary Name	INFUGEM, gemcitabine injection (approved by DMEPA on 05/11/2018)
Dosage forms / Strength	Injection, 10 mg/mL, fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, and 220 mL
Route of Administration	Intravenous use
Proposed Indication(s)	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none"> • in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy • 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 • in combination with cisplatin for the treatment of non-small cell lung cancer • as a single agent for the treatment of pancreatic cancer
Recommended:	Approval

This cross-discipline team leader review is based on the primary reviews, memos, and documented review input of:

- Drug Product (Nina Ni, Ph.D.); in Panorama, dated 10/13/2015
- Drug Product (Nina Ni, Ph.D.); in Panorama, dated 06/13/2018
- Manufacturing Facilities (Thuy Nguyen, Ph.D.); in Panorama, dated 06/13/2018
- Manufacturing Process (Dhanalakshmi Kasi, Ph.D.); in Panorama, dated 03/30/2017
- Clinical (Margit Horiba, M.D., MPH); in DARRTS, dated 10/28/2015
- Clinical (Margit Horiba, M.D., MPH); in DARRTS, dated 7/12/2018
- Clinical Pharmacology (Edwin Chow, Ph.D.); in DARRTS, dated 06/21/2018
- Pharmacology/Toxicology (Alexander Putnam, Ph.D.); in DARRTS, dated 10/14/2015
- DMEPA (Colleen Little, Pharm.D.); in DARRTS, dated 06/13/2018
- DMEPA (Janine Stewart, Pharm.D.); in DARRTS, dated 05/11/2018
- OPDP (Nazia Fatima, Pharm.D.); in DARRTS, dated 07/04/2018

1. Introduction

Sun Pharmaceutical Industries Ltd. (SPIL) submitted NDA 208313 in support of a ready-to-use formulation for gemcitabine. The application is a 505(b)(2) application, referencing the lyophilized (b) (4) formulation, Gemzar (NDA 20509). Gemzar is available in 200 mg and 1 g single dose vials. Gemzar is administered following reconstitution and dilution of the lyophilized powder with 0.9% NaCl. SPIL's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, and 2200 mg gemcitabine in infusion bags with a minitulipe stopper. The formulation contains only the drug substance (gemcitabine hydrochloride), sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to the listed drug, but has the advantage of limited potential for unintentional exposure to healthcare professionals due to the ready-to-use presentation.

2. Background

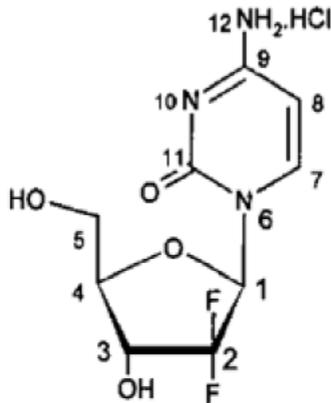
Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy; (2) in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated; (3) in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer.

The current application relies on the Agency's determination of safety and efficacy for the gemcitabine lyophilized powder for injection (Gemzar), which was approved for marketing under NDA 20509 on 05/15/1996. The first review cycle for NDA 208313 resulted in a complete response letter issued 11/24/2015 on the basis of deficiencies at the drug product manufacturing site, a manufacturing process deficiency (b) (4) and a pending human factors study. The 2nd review cycle resolved the manufacturing process deficiency and the human factors study was deemed adequate with changes to the labeling. However, the drug product manufacturing site received a "withhold" recommendation from the OPQ Office of Process and Facilities on 05/10/2017. Accordingly, the recommendation from the review team was again for a complete response during second review cycle for NDA 208313 on 05/23/2017. During the 2nd review cycle, internal labeling review resulted in a substantially complete review of the package insert except for Section 2. The applicant proposed a dosing strategy wherein a patient's dose is banded by possible combinations of single-dose infusion bags. This strategy departs from the dose calculation used in the listed product, Gemzar, which prescribes a defined dose of gemcitabine based on body surface area (BSA). Infugem inherently does not allow precise dosing because the container configurations are only available in 100 mg increments of gemcitabine. In the complete response letter, the applicant was asked to provide justification that the dose banding instructions in Section 2 of the prescribing instructions, which would result in an approximation of the recommended dose, does not affect the safety and efficacy of the drug in its conditions of uses. This dose banding issue was adequately addressed in this review cycle.

The cross disciplinary team lead (CDTL) memo below is abbreviated as there was no new review from the nonclinical or clinical review teams. Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017 for summary of those sections.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance used to formulate the gemcitabine ready-to-use formulation for NDA 208313 is gemcitabine hydrochloride and the active moiety in the drug product is gemcitabine. Labeling and strength designation is on the basis of the gemcitabine free base, consistent with the listed product, Gemzar, and the FDA salt nomenclature policy. Chemical characterization for the drug substance, gemcitabine hydrochloride, is represented below:



A.
2'-deoxy-2',2'-difluorocytidine monohydrochloride
(β - Isomer)
 $C_9H_{11}F_2N_3O_4 \cdot HCl$
MW = 299.66 (salt); 263.20 (base)

Gemcitabine hydrochloride is soluble in aqueous buffers (~100 mg/mL), slightly soluble in methanol, and practically insoluble in alcohol and polar organic solvents. The dissociation constant for gemcitabine at 25°C under most acidic conditions is 11.65 ± 0.70 and a LogP of -2.216 ± 0.487 . Gemcitabine used in the drug product manufacturing process is crystalline form, but given the high solubility of the drug substance and the fact that the drug product is a ready-to-use infusion solution, polymorphic control is not critical. Gemcitabine contains 3 chiral centers and is isolated as the β -anomer. Its optical rotation at 20°C is $43.0^\circ - 50.0^\circ$. The bulk drug substance, gemcitabine hydrochloride, USP is manufactured and supplied by SPIL under DMF 19427. (b) (4)

Information from the open portion of this DMF is captured in the NDA review; however, for further detail about the manufacturing and control of the drug substance, refer to the DMF 19427 review. The applicant controls the drug substance as per the USP monograph for gemcitabine hydrochloride in addition to in-house specifications, which is adequate.

SPIL's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, and

2200 mg gemcitabine in infusion bags with a minitulipe stopper. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to the listed drug. All excipients are compendial grade. A (b) (4) % overfill is part of the drug product design, which was agreed upon at the pre-NDA meeting 12/11/2016 (b) (4). There are no overages in the formulation.

SFIL's presentation is stored in an aluminum overlapping pouch, primarily to contain container closure breaches for this cytotoxic product. Photo stress studies demonstrated that the drug product solution is mildly photolabile and the primary container system, the infusion bag, is sufficient protection from light. The product's strength is labeled on the basis of the gemcitabine free base, as is the listed drug, Gemzar, which is consistent with the salt nomenclature policy. This product is designed to be ready-to-use, to reduce manipulation of the product prior to administration, decreasing exposure of the active to healthcare providers, reducing the potential for microbial contamination during dose preparation and potentially reducing medication errors with regards to dose preparation.

The manufacturing process

(b) (4)



The applicant's risk mitigation efforts are adequate and this issued is resolved.

Reduced, bracketed stability data using the three batches of the 120, 160, 180, 200, and 220 mL fill volumes was provided to support a 24-month shelf life for the drug product. One batch each of the 130, 140, 150, 170, and 190 mL fill volumes was placed on stability. Since the same bulk solution is used to fill the infusion bags, this bracketing design is acceptable. 6 months accelerated and 18 months long term stability data is available for 120, 130, 140, 150, 160, 170, 180, 190, 200, and 220 mL fill volume. 24 months long term stability data is also available for 120 mL fill volume. The only notable trend on stability was an increase in degradation to dFDU, especially under accelerated stability conditions. A 24-month shelf life may be granted for the product when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] based on the real-time stability data (for 120 mL fill volume) as well as statistical analysis.

Facilities: The Office of Pharmaceutical Quality recommended a complete response action for

NDA 208313 during the first and second review cycles based on an inadequate status of the testing and manufacturing facilities and one manufacturing process deficiency. The drug product manufacturing site, Sun Pharmaceutical Industries Ltd (FEI 3002809586), received a withhold recommendation because its cGMP status was Official Action Indicated (OAI). The same site was inspected from September 8-16, 2015 and classified as OAI. This was a cGMP inspection and PAI coverage for [REDACTED] ^{(b) (4)}. The inspection resulted in a Warning Letter issued to the site on 12/17/2015. The site was re-inspected from November 17, 2016 to December 1, 2016 and the initial classification was OAI. A regulatory meeting was held between OC/OMQ and the applicant on 05/09/2017 to discuss the outstanding cGMP compliance issues. The facility's compliance status remains as OAI after the regulatory meeting. The site was re-inspected again from February 12, 2018 to February 23, 2018 with the initial classification of OAI and re-classified to VAI by OMQ. The site has acceptable SVS profile. Based on the latest inspection result, Sun Pharmaceutical Industries Limited, FEI: 3002809586, the proposed drug product manufacturing and testing facility, is found to be acceptable for the operations listed in NDA 208313-ORIG-1-Resub-23.

4. Product Quality Microbiology

Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017.

5. Biopharmaceutics

Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017.

Overall CMC Recommendation: No outstanding or additional CMC issues are identified during this review cycle. The Office of Pharmaceutical Quality recommends "Approval" for this NDA 208313.

6. Clinical Pharmacology

Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017. In this re-submission (SDN 23 and SDN 25), the pharmacokinetics of gemcitabine as reported in the literature (refs) and additional supportive PK simulations using a gemcitabine population pharmacokinetic (PopPK) model from the literature submitted by Sun (SDN 1, 20, and 25) are reviewed to further provide supportive evidence that a difference in the absolute dose between Gemzar[®] and Infugem of up to 5% would not lead to clinical meaningful differences in efficacy and safety. The clinical pharmacology review filed in DARRTS on 06/21/2018 provides a thorough review of the pharmacokinetic (PK) data from the listed product and published literature. The clinical pharmacology team determined that the proposed formulation, that requires the dose to be rounded to the nearest intended dose, results in a maximum difference in dose of 5% compared to Gemzar[®]. This difference in absolute dose is determined not to result in clinically relevant differences in gemcitabine exposure when comparing Gemzar[®] and Infugem.

7. Non-Clinical Pharmacology/Toxicology

Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017.

8. Clinical/Statistical-Efficacy

Refer to the previous CDTL memos filed 10/21/2015 and 05/16/2017.

No new clinical data were provided with this submission, as no clinical studies were done for this 505(b)(2) application. No clinical issues were identified. The applicant proposes a dose banding strategy because the container configuration of the drug product does not allow precise dosing. The applicant provided adequate justification on this strategy in light of potential clinical safety or efficacy impacts of dose banding compared to precise dose administration. Please refer to clinical pharmacology review filed on 06/21/2018.

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling and Human Factors Review

The labeling review was performed by DMEPA, CMC, OPDP, and the DOP2 clinical review team. In the SDN 30, dated 07/05/2018, the applicant, Sun provided justification for maintaining the tamper evident language in both PI and IFU. The provided justification was found adequate by CMC and the DOP2 clinical review team.

CMC Recommendations: No comments

Clinical Recommendations: No comments

Clinical Pharmacology Recommendations:

Only relevant clinical pharmacology sections are included. The Applicant's proposed labeling change are in BLUE and modifications are made by the Agency in RED.

1. Section 2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of INFUGEM is 1000 mg/m² as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after INFUGEM administration on Day 1 of each 21-day cycle. Select the INFUGEM premixed bag(s) that allow for a variance of up to 5% of the BSA-calculated dose as described in Table 5 [see Dosage and Administration (2.6)].

2. Section 2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of INFUGEM is 1250 mg/m² intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m² on Day 1 as a 3-hour intravenous infusion before INFUGEM administration. Select the

INFUGEM premixed bag(s) that allow for a variance of up to 5% of the BSA-calculated dose as described in Table 5 [see Dosage and Administration (2.6)].

OPDP Recommendations: No comments

DMEPA Recommendations:

1. General Comments (Container labels, Overwrap Labeling & Carton Labeling)
 - a. 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.
 - For the expiration date, we recommend using a format such as MMMYYYY (e.g. JAN2019) or MMDDYYYY (e.g. JAN312019) to minimize confusion and reduce the risk for deteriorated drug medication errors.
 - b. Revise the package type term from (b)(4) to “single-dose bag” on container labels and overwrap and carton labeling.
2. Container Labels & Carton Labeling
 - a. Remove (b)(4)
3. Container Labels
 - a. 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.
4. Instructions for Use (IFU)
 - a. For consistency across labeling, consider replacing the statement, (b)(4) with “Instructions for Use: Selecting the Correct Infugem Bag(s).”
 - b. For consistency across labeling, replace the statement, “INFUGEM for intravenous use is a clear, colorless, (b)(4),” with the statement, (b)(4) Do NOT remove or add medication.” which is proposed on the infusion bag label.
 - c. 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.”
 - d. 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)
 - e. 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).
 - f. Change the section, “Instructions for Use: Spiking the Bag” to read, “Preparation and Administration” and include instruction on how to infuse two infusion bags.

All above labeling comments were conveyed to the applicant and adequately addressed by the applicant.

In the 2nd review cycle, the dose banding issue was recommended to be revisited. Refer to the CDTL memo filed 05/16/2017. In this review cycle, the dose banding issue was satisfactorily resolved. Please refer to clinical pharmacology's review filed on 06/21/2018.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Gemzar, when the listed product is reconstituted and diluted for administration. No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommends an **Approval** for the application.

- **Risk Benefit Assessment**

Please refer to NDA 020509.

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/

NINA NI
07/16/2018

JOSEPH E GOOTENBERG
07/16/2018

I agree with the conclusions reached by the CDTL, as embodied in this review. I recommend that this NDA be issued an APPROVAL

Cross-Discipline Team Leader Review

Date	16-May-2017
From	Olen Stephens, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208-313
Type of Application	505(b)(2) – complete response resubmission
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Date of Receipt	23-November-2016
PDUFA Goal Date	30-May-2017
Proposed Proprietary Name	INFUGEM, gemcitabine injection (approved by DMEPA 14-Feb-17)
Dosage forms / Strength	Injection 10 mg/mL, fill volumes of 120, 130, 140, 150,160, 170, 180, 190, 200, (b)(4) 220 mL
Route of Administration	Injection
Proposed Indication(s)	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none"> • in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy • 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 • in combination with cisplatin for the treatment of non-small cell lung cancer • as a single agent for the treatment of pancreatic cancer
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (Nina Ni, Ph.D.); in Panorama, dated 13-Oct-2015
- Manufacturing Facilities (Thuy Nguyen, Ph.D.); in Panorama, dated 10-May-2017
- Manufacturing Process (Dhanalakshmi Kasi, Ph.D.); in Panorama, dated 30-Mar-2017
- Clinical (Margit Horiba, M.D., MPH); in DARRTS, dated 28-Oct-2015
- Clinical Pharmacology (Jun Yang, Ph.D.); in DARRTS, dated 21-Oct-2015
- Pharmacology/Toxicology (Alexander Putnam, Ph.D.); in DARRTS, dated 14-Oct-15
- DMEPA (Otto Townsend, Pharm.D.); in DARRTS, dated 17-Apr-2017

1. Introduction

Sun Pharmaceutical Industries Ltd. (SPIL) submitted NDA 208-313 in support of a ready-to-use formulation for gemcitabine. The application is a 505(b)(2) application, referencing the lyophilized (b) (4) formulation, Gemzar (NDA 20-509). Gemzar is available in 200 mg and 1 g single dose vials. Gemzar is administered following reconstitution and dilution of the lyophilized powder with 0.9% NaCl. SPIL's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b) (4) and 2200 mg gemcitabine in infusion bags with a minitulipec stopper. The formulation contains only the drug substance (gemcitabine hydrochloride), sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to the listed drug, but has the advantage of limited potential for unintentional exposure to healthcare professionals due to the ready-to-use presentation.

2. Background

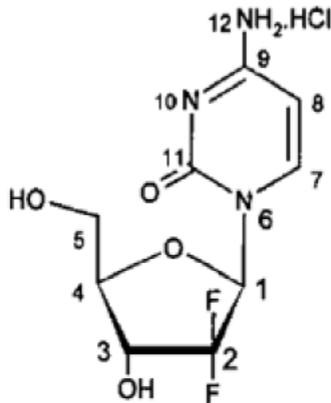
Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy; (2) in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated; (3) in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer.

The current application relies on the Agency's determination of safety and efficacy for the gemcitabine lyophilized powder for injection (Gemzar), which was approved for marketing under NDA 20-509 on 15-May-1996. The first review cycle for NDA 208-313 resulted in a complete response letter issued 24-Nov-2015 on the basis of deficiencies at the drug product manufacturing site, a manufacturing process deficiency (b) (4) and a pending human factors study. The current review cycle resolved the manufacturing process deficiency and the human factors study was deemed adequate with changes to the labeling. However, the drug product manufacturing site received a "withhold" recommendation from the OPQ Office of Process and Facilities on 10-May-2017, so the recommendation from the review team is again for a complete response. Internal labeling review resulted in a substantially complete review of the package insert except for Section 2. The applicant proposes a dosing strategy wherein a patient's dose is banded by possible combinations of single-dose infusion bags. This strategy departs from the dose calculation used in the listed product, GEMZAR, which prescribes a defined dose of gemcitabine based on body surface area (BSA). INFUGEM inherently does not allow precise dosing because the container configurations are only available in 100 mg increments of gemcitabine. In the complete response letter, the applicant is asked to provide justification that the dose banding instructions in Section 2 of the prescribing instructions, which would result in an approximation of the recommended dose, does not affect the safety and efficacy of the drug in its conditions of uses. This is an on-going review issue that will be addressed in future resubmissions of this NDA.

The cross disciplinary team lead (CDTL) memo below is abbreviated as there was no new review from the nonclinical, clinical pharmacology, or clinical review teams. Refer to the previous CDTL memo filed 21-Oct-2015 for summary of those sections.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance used to formulate the gemcitabine ready-to-use formulation for NDA 208-313 is gemcitabine hydrochloride and the active moiety in the drug product is gemcitabine. Labeling and strength designation is on the basis of the gemcitabine free base, consistent with the listed product, Gemzar, and the FDA salt nomenclature policy. Chemical characterization for the drug substance, gemcitabine hydrochloride, is represented below:



A.
2'-deoxy-2',2'-difluorocytidine monohydrochloride
(β - Isomer)
 $C_9H_{11}F_2N_3O_4 \cdot HCl$
MW = 299.66 (salt); 263.20 (base)

Gemcitabine hydrochloride is soluble in aqueous buffers (~100 mg/mL), slightly soluble in methanol, and practically insoluble in alcohol and polar organic solvents. The dissociation constant for gemcitabine at 25 °C under most acidic conditions is 11.65 ± 0.70 and a LogP of -2.216 ± 0.487 . Gemcitabine used in the drug product manufacturing process is crystalline form, but given the high solubility of the drug substance and the fact that the drug product is a ready-to-use infusion solution, polymorphic control is not critical. Gemcitabine contains 3 chiral centers and is isolated as the β -anomer. Its optical rotation at 20°C is $43.0^\circ - 50.0^\circ$. The bulk drug substance, Gemcitabine hydrochloride, USP is manufactured and supplied by SPIL under DMF 19427. (b) (4)

Information from the open portion of this DMF is captured in the NDA review; however, for further detail about the manufacturing and control of the drug substance, refer to the DMF 19427 review. The applicant controls the drug substance as per the USP monograph for gemcitabine hydrochloride in addition to in-house specifications, which is adequate.

SPIL's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b) (4)

(b) (4) and 2200 mg gemcitabine in infusion bags with a minitulipe stopper. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to the listed drug. All excipients are compendial grade. A (b) (4) % overfill is part of the drug product design, which was agreed upon at the pre-NDA meeting (b) (4) 16-Dec-11 (b) (4). There are no overages in the formulation.

SFIL's presentation is stored in an aluminum overlapping pouch, primarily to contain container closure breaches for this cytotoxic product. Photo stress studies demonstrated that the drug product solution is mildly photolabile and the primary container system, the infusion bag, is sufficient protection from light. The product's strength is labeled on the basis of the gemcitabine free base, as is the listed drug, Gemzar, which is consistent with the salt nomenclature policy. This product is designed to be ready-to-use, to reduce manipulation of the product prior to administration, decreasing exposure of the active to healthcare providers, reducing the potential for microbial contamination during dose preparation and potentially reducing medication errors with regards to dose preparation.

The manufacturing process

(b) (4)

(b) (4)

The applicant's risk mitigation efforts are adequate and this issued is resolved.

Reduced, bracketed stability data using the three batches of the 120, 160, 180, 200 and 220 mL fill volumes is provided to support a 24 month shelf life for the drug product. One batch each of the 130, 140, 150, 170, and 190 mL fill volumes was placed on stability. Since the same bulk solution is used to fill the infusion bags, this bracketing design is acceptable. 6 months accelerated and 18 months long term stability data is available for 120, 130, 140, 150, 160, 170, 180, 190, 200, and 220 mL fill volume. 24 months long term stability data is also available for 120 mL fill volume. The only notable trend on stability was an increase in degradation to dFDU, especially under accelerated stability conditions. A 24 month shelf life may be granted for the product when stored at 25°C (77°F) including excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] based on the real time stability data (for 120 mL fill volume) as well as statistical analysis.

Facilities: As noted above, a complete response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer. The drug product manufacturing site, Sun Pharmaceutical Industries Ltd (FEI 3002809586), received a withhold recommendation because its CGMP status was Official Action Indicated (OAI). This site was inspected September 8-16, 2014, and this inspection resulted in a Warning Letter issued to the firm on December 17, 2015. The firm was re-inspected from November 17, 2016 to December 1, 2016 and the initial classification was OAI. A regulatory meeting was held between OC/OMQ and the firm on May 9, 2017 to discuss the outstanding cGMP compliance issues. The facility's compliance status remained OAI after the regulatory meeting.

4. Product Quality Microbiology

Refer to the previous CDTL memo filed 21-Oct-2015

5. Biopharmaceutics

Refer to the previous CDTL memo filed 21-Oct-2015

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends a **complete response** action for NDA 208-313 on the basis of an inadequate status of the testing and manufacturing facilities (10-May-17). The Sun Pharmaceutical Industries Ltd (FEI 3002809586) small volume sterile fill site received a withhold recommendation, with an Official Action Indicated.

The following Facility Deficiency should be conveyed in the Complete Response letter:

Deficiency: "During a recent inspection of the Sun Pharmaceutical Industries Limited, FEI: 3002809586, manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved."

6. Clinical Pharmacology

Refer to the previous CDTL memo filed 21-Oct-2015

7. Non-Clinical Pharmacology/Toxicology

Refer to the previous CDTL memo filed 21-Oct-2015

8. Clinical/Statistical-Efficacy

Refer to the previous CDTL memo filed 21-Oct-2015

No new clinical data were provided with this submission, as no clinical studies were done for this 505(b)(2) application. The clinical review recommendation is to not approve the application based

on deficiencies identified by Quality review staff (i.e., related to facilities). No clinical issues were identified; however, labeling review will continue through the next NDA submission. Of particular note, the applicant proposes a dose banding strategy because the container configuration of the drug product does not allow precise dosing. The applicant will be asked in the complete response letter to justify this strategy in light of potential clinical safety or efficacy impacts of dose banding compared to precise dose administration.

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling and Human Factors Review

The DMEPA review includes evaluation of the Human Factors (HF) validation study report for selection of dose strengths, proposed container labels, proposed carton labeling, proposed Prescribing Information (PI) and proposed Instructions for Use (IFU). 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 completed human factors testing to validate that users can select the appropriate product (i.e., strength) when presented with an order for gemcitabine.

During the first review cycle, SPIL submitted the protocol for the human factors study regarding dose selection. DMEPA sent recommendations regarding the protocol to the applicant in the complete response letter for the first review cycle. In this resubmission, the applicant addressed DMEPA's recommendations enumerated in the complete response letter, so there were no concerns regarding the study protocol. The validation study results were reviewed by DMEPA in the current review cycle.

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 was given a dose card and assigned a 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 was provided 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. During internal labeling review, DMEPA provided additional recommendations in section 5.1 to further optimize the presentation of these two tables. These edits have not been sent to the applicant, but should be retained for future resubmissions.

The HF study included tasks to assess the effectiveness of the 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. 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. Based on the results of this section of the HF study, DMEPA made additional recommendations during internal labelling discussions in section 5.1 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) 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. The user would select the appropriate bag(s) strength based on the patient's BSA and prescribed dose (mg/m²) based on predetermined dose banding (rounding). 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, DMEPA recommends that during labeling negotiations, 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.

SPIL's proposed use of 'dose-banding' involves rounding the prescribed dose to a dose that can be administered using one or a combination of the 10 available bag strengths. The issue of dose banding was referred to CDER's Labeling Coordinating Committee via Ann Marie Trentacosti to set high level expectations for a class of products that are presented as pre-filled infusion bags that may need a dose banding approach. The Coordinating Committee deferred to the clinical division to determine if there is sufficient clinical data to support dose ranges and concluded this is not a labeling issue.

This dose banding strategy also departs from the dose calculation used in the listed product, GEMZAR, which prescribes a defined dose of gemcitabine based on the patient's BSA. INFUGEM inherently does not allow precise dosing because the container configurations are only

available in 100 mg increments of gemcitabine. In the complete response letter, the applicant will be asked to provide justification that the dose banding instructions in Section 2 of the prescribing instructions, which would result in an inherent approximation of the recommended dose, does not affect the safety and efficacy of the drug in its conditions of uses.

Upon resubmission, this dose banding issue will need to be revisited. The division initiated a preliminary consult the Office of Regulatory Policy to identify any potential legal implications of introducing a dose band for a 505(b)(2) application that relies on the clinical data from an innovator product with defined dosing levels. A finalized response is not available at the time of the complete response action date.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Gemzar, when the listed product is reconstituted and diluted for administration. No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommendation is for a **complete response** to the application based on inadequate facilities inspections. When the NDA is resubmitted, the applicant's dose banding strategy will need to be discussed with ORP to confirm there are no legal impediments to relying on data for the listed drug, which prescribes a precise dose.

- **Risk Benefit Assessment**

Please refer to NDA 020509.

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/s/

OLEN M STEPHENS

05/16/2017

CDTL recommendation: complete response

Cross-Discipline Team Leader Review

Date	21-Aug-2015
From	Olen Stephens, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208-313
Type of Application	505(b)(2)
Applicant	Sun Pharmaceuticals Ltd.
Date of Receipt	29-March-2015
PDUFA Goal Date	30-March-2015
Proposed Proprietary Name	Gemcitabine Injection
Dosage forms / Strength	Injection 10 mg/mL, fill volumes of 120, 130, 140, 150,160, 170, 180, 190, 200, (b)(4)220 mL
Route of Administration	Injection
Proposed Indication(s)	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none"> • in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy • in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (Nina Ni, Ph.D.); in Panorama, dated 13-Oct-2015
- Drug Substance (Sharon Kelly, Ph.D.); in Panorama, dated 13-Oct-2015
- Microbiology (Helen Ngai, Ph.D.); in DARRTS, dated 13-Oct-2015
- Manufacturing Facilities (Thuy Nguyen, Ph.D.); in Panorama, dated 13-Oct-2015
- Manufacturing Process (Dhanalakshmi Kasi, Ph.D.); in Panorama, dated 13-Oct-2015
- Clinical (Margit Horiba, M.D., MPH); in DARRTS, dated 9-Oct-2015
- Clinical Pharmacology (Jun Yang, Ph.D.); in DARRTS, dated 21-Oct-2015
- Pharmacology/Toxicology (Alexander Putnam, Ph.D.); in DARRTS, dated 14-Oct-15

- DMEPA (Otto Townsend, Pharm.D.); in DARRTS, dated 11-Sep-2015
- Quality Biopharmaceutics (Om Anand, Ph.D.); in Panorama, dated 13-Oct-2015

1. Introduction

Sun Pharmaceutical Industries Ltd. has submitted NDA 208-313 in support of a ready-to-use formulation for gemcitabine. The application is a 505(b)(2) application, referencing the lyophilized (b)(4) formulation, Gemzar (NDA 20-509). Gemzar is available in 200 mg and 1 g single dose vials. Gemzar is administered by reconstituting and diluting the lyophilized powder with 0.9% NaCl. Sun's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b)(4) and 2200 mg gemcitabine in infusion bags with a minitulipe stopper. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b)(4) such that the administered solution is nearly identical to the listed drug.

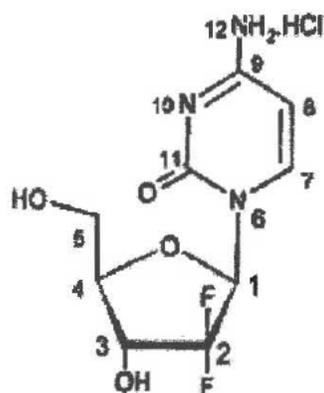
2. Background

Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy; (2) 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; (3) in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer

The current application relies on the Agency's determination of safety and efficacy for the gemcitabine lyophilized powder for injection (Gemzar), which have been previously approved for marketing under NDA 20-509 on 15-May-1996.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208313 is gemcitabine. Labeling and strength designation is on the basis of the gemcitabine free base, consistent with the listed product, Gemzar, and the FDA salt nomenclature policy. The active ingredient used to formulate the gemcitabine ready-to-use formulation is gemcitabine hydrochloride:



A.
 2'-deoxy-2',2'-difluorocytidine monohydrochloride
 (β - Isomer)
 $C_9H_{11}F_2N_3O_4 \cdot HCl$
 MW = 299.66 (salt); 263.20 (base)

Gemcitabine hydrochloride is soluble in aqueous buffers (~100 mg/mL), slightly soluble in methanol, and practically insoluble in alcohol and polar organic solvents. The dissociation constant for gemcitabine at 25 °C under most acidic conditions is 11.65 ± 0.70 and a LogP of -2.216 ± 0.487 . Gemcitabine used in the drug product manufacturing process is crystalline form, but given the high solubility of the drug substance and the fact that the drug product is a ready-to-use infusion solution, polymorphic control is not critical. Gemcitabine contains 3 chiral centers and is isolated as the β -anomer. Its optical rotation at 20°C is $43.0^\circ - 50.0^\circ$. The bulk drug substance, Gemcitabine hydrochloride, USP is manufactured and supplied by Sun Pharmaceutical Industries Ltd. under DMF 19427. (b) (4)

Information from the open portion of this DMF is captured in the NDA review below; however, for further detail about the manufacturing and control of the drug substance, refer to the DMF 19427 review. The applicant controls the drug substance as per the USP monograph for gemcitabine hydrochloride in addition to in-house specifications, which has been deemed adequate.

Sun's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b) (4) and 2200 mg gemcitabine in infusion bags with a minitulipe stopper. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment. (b) (4)

such that the administered solution is nearly identical to the listed drug. All excipients are compendial grade. A (b) (4)% overfill is part of the drug product design, which was agreed upon at the pre-NDA meeting 16-Dec-11 (b) (4) There are no overages in the formulation.

Sun's presentation is stored in an aluminum overlapping pouch, primarily to contain container closure breaches for this cytotoxic product. Photo stress studies demonstrated that though the drug product solution is mildly photolabile, the primary container system, the infusion bag, is sufficient protection from light. The product's strength is labeled on the basis of the gemcitabine free base, as is the listed drug, Gemzar, which is consistent with the salt nomenclature policy. This product is

designed to be ready-to-use, to reduce manipulation of the product prior to administration, decreasing exposure of the active to healthcare providers, reducing the potential for microbial contamination during dose preparation and reducing medication errors with regards to dose preparation.

The manufacturing process

(b) (4)

A single deficiency will be included in the complete response letter regarding this issue (see below). After visual inspection, the infusion bags are labeled and packaged in an aluminum overwrap.

Because the product is (b) (4) in the infusion bag, container compatibility is a major risk. The drug product reviewer evaluated the extractable/leachable studies, ink migration studies, and risk mitigation approach by Sun Pharmaceuticals Ltd. and determined the container closure system is adequately compatible with this drug product.

The drug product impurity levels are controlled as per the USP monograph with the following exceptions.

(b) (4)

ICH Q3D has not been fully implemented, but in anticipation of applying these quality standards for elemental impurities for all applications, an information request was sent to obtain a formal risk assessment. The risk assessment identified potential sources of elemental impurities and evaluated the measured levels for these elemental impurities against the permitted daily exposure (PDE) limits as defined in ICH Q3D. The analysis demonstrated that the risk of elemental impurities in this product is low and that the measured amounts in current batches is well below the PDE.

The drug product reviewer noted that literature sources have identified

(b) (4)

(b) (4)

NDA 208313 is a solution ready for infusion. The applicant was asked to justify the absence of controls for these impurities. In response, the applicant provided analytical data of heat stressed samples, with UV detection at 205 nm. The studies demonstrate that because of the relatively neutral pH of the drug product solution, these impurities do not require active control in the specifications.

Reduced, bracketed stability data using the three batches of the 120, 160, 180, 200 and 220 mL fill volumes is provided to support a 24 month shelf life for the drug product. One batch each of the 130, 140, 150, 170, and 190 mL fill volumes was placed on stability. Since the same bulk solution is used to fill the infusion bags, this bracketing design is acceptable. 6 months accelerated and 18 months long term stability data is available for 120, 130, 140, 150, 160, 170, 180, 190, 200, and 220 mL fill volume. 24 months long term stability data is also available for 120 mL fill volume. The only notable trend on stability was an increase in degradation to dFDU, especially under accelerated stability conditions. A 24 month shelf life may be granted for the product when stored at 25°C (77°F) including excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] based on the real time stability data (for 120 mL fill volume) as well as statistical analysis.

Facilities: As noted above a complete response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer, Thuy Nguyen and review deficiency by Dhanalakshmi Kasi. The drug substance manufacturing and testing site, Sun Pharmaceutical Industries, Ltd. (FEI 3003227153) was acceptable based on profile; it was last inspected 19-Jun-15 and received an initial evaluation of VAI status. The drug product manufacturing, packaging, release, and stability testing site, Sun Pharmaceuticals Industries, Ltd (FEI 3002809586) received an initial OAI status and a compliance action is pending. This site was last inspected 8-16-Sep-14, which resulted in an OAI classification based on the issuance of a FDA-483 with 23 observations. The Office of Compliance is currently working on issuing a warning letter for this site. A manufacturing process deficiency [REDACTED] (b) (4) [REDACTED] will also be sent with the complete response letter. NDA 208313 cannot be recommended for approval at this time.

Risk Management:

The manufacturing process [REDACTED] (b) (4)

[REDACTED]

However, the fact that this NDA is receiving a complete response action based on inadequate evaluations of the manufacturing and testing facilities raises concerns over the quality management system [REDACTED] (b) (4). As a post-action risk management step, the review team requests that the inspection team (ORA and DIA) evaluate the quality management's [REDACTED] (b) (4).

4. Product Quality Microbiology

(b) (4)

The drug product specification includes bacterial endotoxins testing and sterility testing as per USP <85> and USP <71>, respectively. The validation of the (b) (4) process has been deemed adequate and no pending microbiological concerns remain for the NDA.

5. Biopharmaceutics

The Division of Biopharmaceutics evaluated the overall information supporting the biowaiver request and this information is acceptable. The biowaiver was requested on account of the exclusion of the (b) (4) mannitol and (b) (4) sodium acetate. These differences are not expected to have an impact on the disposition of gemcitabine from the Applicant's proposed formulation as compared to the listed product. Therefore, the sponsor's request for a waiver of the in vivo study for their proposed product is granted.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends a **complete response** action for NDA 208-313 on the basis of an inadequate status of the testing and manufacturing facilities (5-Aug-15) and one manufacturing process deficiency. The Sun Pharmaceutical Industries Ltd (FEI 3002809586) small volume sterile fill site received a withhold recommendation, with an Official Action Indicated (24-Feb-15). There is one review deficiency related to the manufacturing process, which will be included in the complete response letter.

(b) (4)

6. Clinical Pharmacology

Sun Pharmaceutical Industries submitted a NDA for "ready-to-infuse" formulation of GemcitabineHydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL under Section 505(b)(2). Gemzar (Gemcitabine Hydrochloride) is the listed Drug (NDA 20,509; approved in 1996 for 200 mg/vial and 1 g/vial). The proposed indication, dose, route, and duration of administration for Sun Pharmaceutical product are the same as those of Gemzar and the approval will be primarily based on publicly available information for Gemzar.

The primary differences in composition of the solutions to be administered as intravenous infusion between the two products are the presence of mannitol and sodium acetate in the listed drug, but not

in Sun's product. In the current NDA submission, Sun Pharmaceutical Industries requests a waiver of *in vivo* bioequivalence (BE) studies between the proposed product and Gemzar. Sun Pharmaceutical Industries has not conducted or sponsored any clinical pharmacokinetic or BE study to support this NDA. Thus, a clinical pharmacology review is not warranted and there are no clinical pharmacology issues if the applicant's biowaiver request will be granted (See details in the review from OPQ).

7. Non-Clinical Pharmacology/Toxicology

The proposed indication, dose, route, and duration of administration of Sun Pharmaceutical Industries Ltd. Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL will be the same as those of the listed drug, Gemzar®, and thus, reliance on the pharmacology/toxicology information required for the approval of this product is based on previous FDA findings for the safety of the listed drug. Sun Pharmaceutical Industries Ltd. has not conducted or sponsored any non-clinical pharmacokinetic or toxicology studies for this NDA, including any non-clinical studies to support changes in the impurity profile compared to the listed drug or the use of novel excipients. Thus, a pharmacology and toxicology review is not warranted and there are no pharmacology/toxicology issues that would impact the acceptability of this application or the approval of this product at this time.

8. Clinical/Statistical-Efficacy

The proposed indication, dose, route, and duration of administration of Sun Pharmaceutical Industries Limited's Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, will be the same as those of the listed product, Gemzar. As with Gemzar, the product is intended solely for administration by intravenous injection over 30 minutes. At the fixed concentration of 10 mg/mL, the product requires no dilution and is ready to use.

1. Ovarian Cancer: 1,000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
2. Breast Cancer: 1,250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
3. Non-Small Cell Lung Cancer: 1,000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1,250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
4. Pancreatic Cancer: 1,000 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.

Contraindications:

As for Gemzar, gemcitabine hydrochloride in sodium chloride injection is contraindicated in patients with a known hypersensitivity to gemcitabine.

Warnings and Precautions:

As for Gemzar, warnings and precautions are schedule-dependent toxicity (infusion time beyond 60 minutes), myelosuppression (neutropenia, anemia, thrombocytopenia), pulmonary toxicity and respiratory failure, hemolytic uremic syndrome, hepatic toxicity, embryofetal toxicity, exacerbation of radiation therapy toxicity, capillary leak syndrome, posterior reversible encephalopathy syndrome.

Adverse Reactions:

As for Gemzar, the most common (≥20%) adverse reactions of single-agent gemcitabine hydrochloride are nausea/vomiting, anemia, increased ALT, increased AST, neutropenia,

increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

The applicant's product, gemcitabine hydrochloride, differs from Gemzar in that the applicant's product requires no prior dilution and is ready to use. Because the increments of the presentation differ by 100mg from 1200mg to 2000mg, and by 200mg from 2000mg to 2200mg, dose- rounding will be necessary. With the available presentations, rounding will not result in a change of more than 5% of the total calculated dose.

Because Gemzar is available only in 200 mg and 1000 mg vials, it is a common practice in US infusion center pharmacies to round to the nearest vial size with the goal of cost-containment. In fact, a guideline to facilitate the introduction of dose-banding into hospitals in England and Wales was published by the Cancer Network Pharmacists Forum (CNPF) in August 2008. It is the CNPF's opinion that within 5%, "dose banding does not add significantly to the level of imprecision inherent in BSA-based dose calculations nor significantly alter the dose-density of chemotherapy administered over a treatment course. The quantifiable service and patient benefits achieved by banding outweigh any theoretical disadvantages." While a similar document has not been published in the US, it is generally accepted that a difference within 5% will not affect safety or efficacy.

Other differences between the sponsor's product and Gemzar (listed below) are not expected to result in clinically meaningful differences:

1. Inactive ingredients are present in different concentrations.
2. Gemzar contains mannitol and sodium acetate (b)(4) in the lyophilized powder and neither is present in Sun's formulation.

No new clinical data were provided with this submission, as no clinical studies were done for this 505(b)(2) application. The clinical review recommendation is to not approve the application based on deficiencies identified by Quality review staff (i.e., related to facilities). No clinical issues were identified; however, that would preclude approval, contingent upon agreement upon labeling.

9. Safety N/A

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

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.

SPIL 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. 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)


The container labels, overwrap and carton labeling, and PI can be further improved to promote safe use of the product. Labeling was not discussed this review cycle, however. When the NDA is ready for approval, the following comment should be sent to SPIL:

Assigning National Drug Codes (NDC) (b) (4)

To better differentiate National Drug Codes, thus differentiate the different strengths, we recommend changing the product codes (b) (4)

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:

“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, or provide rationale for including the BSA and Target Dose in the IFU.

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)

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."

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Gemzar, when the listed product is reconstituted and diluted for administration. No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommendation is for a **complete response** to the application based on deficiencies identified by Quality review staff, related to inadequate facilities inspections and a manufacturing process deficiency.

- **Risk Benefit Assessment**

Please refer to NDA 020509.

Olen
Stephens -S

Digitally signed by Olen Stephens-S
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ou=FDA, ou=People, cn=Olen Stephens
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