

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

**NDA 208313
Review 3**

Drug Name/Dosage Form	Gemcitabine Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Karin A. Kook, Ph.D.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0023	02/16/2018	Resubmission

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Product	Nina Ni	OPQ/ONDP/ONDPI/NDPBII
Process	Dhanalakshmi Kasi	OPQ/ONDP/DNDPII/NDPBVI
Facility	Thuy Nguyen	OPQ/OPF/DIA/IABI
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO/DRBPMI/RBMBI
Application Technical Lead	Nina Ni	OPQ/ONDP/DNDPI/NDPBII
Environmental Analysis (EA)	Olen Stephens	OPQ/ONDP/DNDPI/NDPBII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	Type	Item	Status	Date Review Completed	Comments
	Type II		Adequate	25-Feb-16	Neeraj Chopra
(b) (4)	Type III	(b) (4)	N/A		
	Type III		N/A		
	Type III		N/A		
	Type III		N/A		

Other Document Applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	208313	Complete Response Letter; 05/23/2017

2. CONSULTS: None

Executive Summary

I. Recommendations and Conclusion on Approvability

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 manufacturing deficiency was satisfactorily resolved during the 2nd review cycle. 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 (b) (4). The inspection resulted in a Warning Letter issued to the site on December 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 May 9, 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.

No outstanding or additional CMC issues are identified during this review cycle. The Office of Pharmaceutical Quality recommends “**Approval**” for this NDA 208313.

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

None

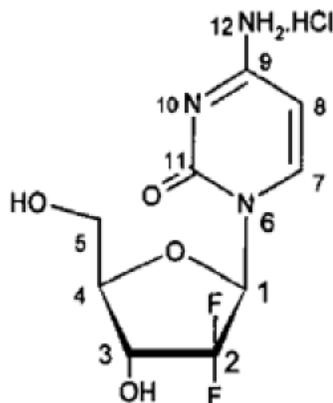
II. Summary of Quality Assessments

A. Product Overview

Drug Substance [Gemcitabine Hydrochloride] Quality Summary

There is no new drug substance information provided in this resubmission. Thus, there is no drug substance review conducted in this review.

The drug substance for NDA 208313 is gemcitabine hydrochloride. 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:



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 it has 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)

(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.

Drug Product [Gemcitabine in Sodium Chloride Injection] Quality Summary

There is no new drug product information provided in this resubmission. Thus, there is no drug product review conducted in this review.

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 20509). 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, and 2200 mg gemcitabine in infusion bags with a minitilipe 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,

(b)(4)
(b)(4)

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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. 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

(b) (4)
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(b) (4)
(b) (4)

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 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 Summary

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 (b) (4). The inspection resulted in a Warning Letter issued to the site on December 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 May 9, 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.

Proprietary Name of the Drug Product	<i>INFUGEM</i>
Non Proprietary Name of Drug Product	<i>Gemcitabine Injection</i>
Proposed Indication(s) including Intended Patient Population	<p><i>Gemcitabine is a nucleoside metabolic inhibitor indicated:</i></p> <ul style="list-style-type: none"> • <i>In combination with carboplatin for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy</i> • <i>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines where clinically contraindicated</i> • <i>In combination with cisplatin for the treatment of non-small cell lung cancer</i> • <i>As a single agent for the treatment of pancreatic cancer</i>
Duration of Treatment	<i>Until disease progression</i>
Maximum Daily Dose	<i>1,000 mg/m²</i>
Alternative Methods of Administration	<i>NA</i>

Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: Based on the information provided by the Applicant Gemcitabine is soluble in water.
- Drug Product: Since this product is a parenteral solution, BCS classification is not applicable.

2. Biowaivers/Biostudies

- Biowaiver Requests: Exclusion of the (b) (4), mannitol and the (b) (4) sodium acetate, is not expected to have an impact on the disposition of gemcitabine from the Applicant's proposed formulation as compared to the reference formulation. Therefore, the sponsor's request for a waiver of the in vivo study for their proposed product is granted.
- PK studies: N/A
- IVIVC: N/A

B. Special Product Quality Labeling Recommendations

Refer to the labeling review by Nina Ni, the drug product reviewer. The clinical review team completed an initial review of the package insert and container labels.

Recommendations will be conveyed to the applicant prior to approval of this NDA.

C. Final Risk Assessment for Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking		Final Risk Evaluation	Lifecycle Considerations/ Comments
Sterility	Formulation Container Closure Process Parameters Scale/Equipment Site	High	(b) (4)	Acceptable	None
Endotoxin	Formulation Container Closure Process Parameters Scale/Equipment Site	High		Acceptable	None

Assay (stability)	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment Site	Low	(b) (4)	Acceptable	None
Uniformity of Dose (Fill Volume)	Formulation Container Closure Process Parameters Scale/Equipment Site	Low		Acceptable	None
Osmolality	Formulation Raw Materials Parameters Scale/Equipment Site	Low		Acceptable	None
Particulate Matter	Formulation Container Closure Process Parameters Raw Materials Scale/Equipment Site	Low		Acceptable	None
Leachables and Extractables	Formulation Container Closure Process Parameters Raw Materials Scale/Equipment Site	Low		Acceptable	None
Appearance	Formulation Container Closure Process Parameters Scale/Equipment Site	Low		Acceptable	None

Nina Ni, Ph.D.,
Acting QAL/ATL
06/14/2018

APPEARS THIS WAY ON ORIGINAL



Nina
Ni

Digitally signed by Nina Ni

Date: 6/14/2018 02:22:51PM

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BIOPHARMACEUTICS REVIEW for NDA SUBMISSIONS	
Application No.	NDA 208313-ORIG-1-RESUB-23
Type of Submission	505(b)(2)
Applicant/Sponsor	Sun Pharmaceuticals.
Product Name	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection
Davison/Office	Division of Oncology Products 2
Dosage Form/Strength	Injection (Intravenous)10 mg/mL
Route of Administration	Injection (Intravenous)
Intended Use	Ovarian cancer, breast cancer, non-small cell lung cancer and pancreatic cancer
Submission Date	March 29, 2015 (Original Submission) February 16, 2018 (CR Response amendment)
Review Date	04/04/2018
Primary Reviewer	Om Anand, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.
Recommendation	Adequate

SUMMARY:

There is no additional Biopharmaceutics related information in the current submission. This abbreviated review makes a correction to the citation of the CFR in the original biopharmaceutics review document (<http://panorama.fda.gov/project/view?ID=5a8d075f00837f2d379c3498f2dbcd45>).

In the review of the original submission, the Applicant’s request for a waiver of the in vivo study for the proposed drug product, Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, was inadvertently granted under 21 CFR 320.22(b)(1)(i).

It is noted that the data and information submitted in the original Application demonstrate that the proposed drug product was adequately bridged to the listed drug; therefore, per 21 CFR 320.24(b)(6), an in vivo pharmacokinetic study is not needed.

From the Biopharmaceutics perspective, NDA-208313 for Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, is recommended for APPROVAL

SIGNATURE BLOCK

Om Anand, Ph.D. [Date: 04/04/2018]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Okpo Eradiri, Ph.D. [Date: 004/06/2018]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ



Om
Anand

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Okponanabofa
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Recommendation: Complete Response

**NDA 208-313
Review 2**

Drug Name/Dosage Form	Gemcitabine Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Karin A. Kook, PhD

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0013	23-Nov-16	Resubmission
0017	19-Apr-17	Labeling
0018	2-May-17	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Product	Nina Ni	OPQ/ONDP/ONDPI/NDPBII
Process	Dhanalakshmi Kasi	OPQ/ONDP/DNDPII/NDPBVI
Facility	Thuy Nguyen	OPQ/OPF/DIA/IABI
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO/DRBPMI/RBMBI
Application Technical Lead	Olen Stephens	OPQ/ONDP/DNDPI/NDPBII
Environmental Analysis (EA)	Olen Stephens	OPQ/ONDP/DNDPI/NDPBII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
19427	Type II	Sun Pharm. Industries	Gemcitabine Hydrochloride, USP	Adequate	25-Feb-16	Neeraj Chopra
(b) (4)	Type III	(b) (4)	(b) (4)	N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	208-313	Complete Response Letter; 24-Nov-15

2. CONSULTS: None

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality recommended a complete response action for NDA 208-313 during the first review cycle on the basis of an inadequate status of the testing and manufacturing facilities and one manufacturing process deficiency. The manufacturing deficiency has been resolved in this review cycle. 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 remains as OAI after the regulatory meeting.

The Office of Pharmaceutical Quality recommends a **complete response** action for NDA 208-313 on the basis the withhold recommendation (10-May-17) for the drug product manufacturing site, Sun Pharmaceutical Industries Ltd (FEI 3002809586).

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."

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

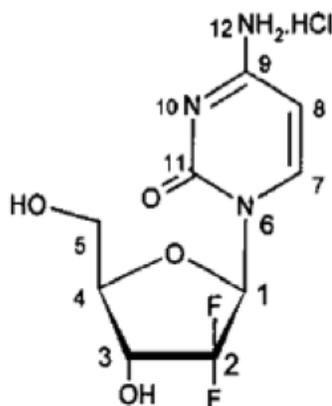
None.

II. Summary of Quality Assessments

A. Product Overview

Drug Substance [Gemcitabine Hydrochloride] Quality Summary

The drug substance for NDA 208313 is gemcitabine hydrochloride. 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:



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 it has 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)

formation 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.

Drug Product [Gemcitabine Injection] Quality Summary

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 20509). 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) (b)(4), such that the administered solution is nearly identical to the listed drug. All excipients are compendial grade. A (b)(4)/(b)(4) overfill is part of the drug product design, which was agreed upon at the pre-NDA meeting 16-Dec-1 (b)(4). There are no overages in

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 i

(b)(4)

(b)(4)

(b) (4)

This product

(b) (4)

(b) (4)

(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. 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)

(b) (4)

(b) (4) An 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.

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.

As noted above a complete response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer, Thuy Nguyen. 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 remains as OAI after the regulatory meeting. NDA 208-313 cannot be recommended for approval at this time.

Proprietary Name of the Drug Product	<i>INFUGEM</i>
Non Proprietary Name of Drug Product	<i>Gemcitabine Injection</i>
Proposed Indication(s) including Intended Patient Population	<p><i>Gemcitabine is a nucleoside metabolic inhibitor indicated:</i></p> <ul style="list-style-type: none"> • <i>In combination with carboplatin for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy</i> • <i>In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines where clinically contraindicated</i> • <i>In combination with cisplatin for the treatment of non-small cell lung cancer</i> • <i>As a single agent for the treatment of pancreatic cancer</i>
Duration of Treatment	<i>Until disease progression</i>
Maximum Daily Dose	<i>1,000 mg/m²</i>
Alternative Methods of Administration	<i>NA</i>

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: Based on the information provided by the Applicant Gemcitabine is soluble in water.
- Drug Product: Since this product is a parenteral solution, BCS classification is not applicable.

2. Biowaivers/Biostudies

- Biowaiver Requests: Exclusion of th ^{(b) (4)} mannitol an ^{(b) (4)} sodium acetate, is not expected to have an impact on the disposition of gemcitabine from the Applicant’s proposed formulation as compared to the reference formulation. Therefore, the sponsor’s request for a waiver of the in vivo study for their proposed product is granted.
- PK studies: N/A
- IVIVC: N/A

B. Special Product Quality Labeling Recommendations

Refer to the labeling review by Nina Ni, the drug product reviewer. The clinical review team completed an initial review of the package insert and container labels. Recommendations will be conveyed to the applicant in anticipation of an NDA resubmission.

C. Final Risk Assessment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Sterility	Formulation Container Closure Process Parameters Scale/Equipment Site	High	^{(b) (4)}	Acceptable	None
Endotoxin	Formulation Container Closure Process Parameters Scale/Equipment Site	High		Acceptable	None

Assay (stability)	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment Site	Low	(b) (4)	Acceptable	None
Uniformity of Dose (Fill Volume)	Formulation Container Closure Process Parameters Scale/Equipment Site	Low		Acceptable	None
Osmolality	Formulation Raw Materials Parameters Scale/Equipment Site	Low		Acceptable	None
Particulate Matter	Formulation Container Closure Process Parameters Raw Materials Scale/Equipment Site	Low		Acceptable	None
Leachables and Extractables	Formulation Container Closure Process Parameters Raw Materials Scale/Equipment Site	Low		Acceptable	None
Appearance	Formulation Container Closure Process Parameters Scale/Equipment Site	Low		Acceptable	None

ATTACHMENT II: List of Deficiencies for Complete Response

A. Facilities Deficiencies

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.

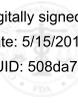
OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date: Olen Stephens 15-May-17



Olen
Stephens

Digitally signed by Olen Stephens
Date: 5/15/2017 02:21:39PM
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Recommendation:

NDA: Approval

NDA 208313 Review # 2

Drug Name/Dosage Form	Gemcitabine HCL in 0.9% Sodium Chloride Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Karin A. Kook, PhD

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Complete Response	23 Nov 2016	CMC

Quality Review Team

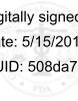
DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	OMPT/CDER/OPQ/ONDP/DNDAPI/NDBI
Drug Product	Nina Ni	OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
Process	Dhanalakshmi Kasi	OMPT/CDER/OPQ/ONDP/DNDPII/NDPBVI
Microbiology	Helen Ngai	OMPT/CDER/OPQ/OPF/DMA/MABI
Facility	Thuy Nguyen	OMPT/CDER/OPQ/OPF/DIA/IABI
Biopharmaceutics	Om Anand	OMPT/CDER/OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steven Kinsley	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Olen Stephens	OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	NA	
ORA Lead	Brooke Higgins	OMPT/CDER/OC/OMQ/DDQI/GCBII
Environmental Assessment (EA)	NA	

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Olen
Stephens

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Recommendation: Complete Response

**NDA 208313
Review # 1**

Drug Name/Dosage Form	Gemcitabine HCL in 0.9% Sodium Chloride Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Karin A. Kook, PhD

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
	March 30, 2015	CMC

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	OPQ/ONDP/NDAPI 1
Drug Product	Nina Ni	OPQ/ONDP/ONDPI/Branch 2
Process	Dhanalakshmi Kasi	OPQ/OPF/Division 3/Branch 7
Microbiology	Helen Ngai	OPQ/OPF/ DMA/ Branch 1
Facility	Thuy Nguyen	OPQ/OPF/ DIA/ Branch 1
Biopharmaceutics	Om Anand	Division of Biopharmaceutics
Regulatory Business Process Manager	Steve Kinsley	OPQ/ OPRO/ Branch 1
Application Technical Lead	Olen Stephens	OPQ/ONDP/ONDPI/Branch 2
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)	Olen Stephens	OPQ/ONDP/ONDPI/Branch 2

Table of Contents

Table of Contents	2
Quality Review Data Sheet.....	3
Executive Summary	4
Primary Quality Review.....	10
ASSESSMENT OF THE DRUG SUBSTANCE	10
2.3.S DRUG SUBSTANCE	10
ASSESSMENT OF THE DRUG PRODUCT	24
2.3.P DRUG PRODUCT	24
R.2 Comparability Protocols.....	74
ASSESSMENT OF THE PROCESS.....	75
2.3.P DRUG PRODUCT	75
R.2 Comparability Protocols.....	114
ASSESSMENT OF THE FACILITIES.....	115
2.3.S DRUG SUBSTANCE	115
2.3.P DRUG PRODUCT	116
ASSESSMENT OF THE BIOPHARMACEUTICS	119
ASSESSMENT OF MICROBIOLOGY	127
2.3.P.7 Container/Closure System.....	127
A APPENDICES	127
A.2 Adventitious Agents Safety Evaluation	127
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	128
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	129
Labeling & Package Insert.....	129
II. List of Deficiencies To Be Communicated.....	139
III. Attachments	139

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
19427	Type II	Sun Pharmaceutical Industries Ltd.	Gemcitabine Hydrochloride, USP	Adequate	Oct. 13, 2015	Sharon Kelly Ph.D.
(b) (4)	Type III	(b) (4)	(b) (4)	N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		

1 Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
pNDA	203-652	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
None				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality recommends a complete response action for NDA 208313 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)

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

The manufacturing proces

(b) (4)

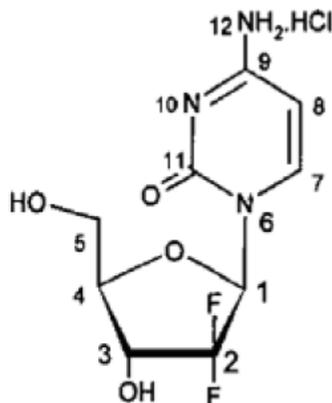
(b) (4)

(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 attempts to control the quality of incoming infusion bags.

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

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:



- B.
C. 2'-deoxy-2',2'-difluorocytidine monohydrochloride
D. (β - Isomer)
E. C₉H₁₁F₂N₃O₄. HCl
F. 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)

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.

B. Drug Product [Established Name] Quality Summary

Sun Pharmaceutical Industries Ltd. has submitted NDA 208313 in support of a ready-to-use formulation for gemcitabine. The application is a 505(b)(2) application, referencing the lyophilize (b)(4) formulation, Gemzar (NDA 20509). 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) (b)(4) such that the administered solution is nearly identical to the listed drug. All excipients are compendial grade. (b)(4)% overfill is part of the drug product design, which was agreed upon at the pre-NDA meeting 16-Dec-11 (b)(4) (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 proces (b)(4)



(b)(4)

(b) (4)

This product i

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(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.

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 (b) (4) will also be sent with the complete response letter. NDA 208313 cannot be recommended for approval at this time.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Gemcitabine Injection
Non Proprietary Name of the Drug Product	Gemcitabine Injection
Non Proprietary Name of the Drug Substance	Gemcitabine
Proposed Indication(s) including Intended Patient Population	<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

	<p>were clinically contraindicated</p> <ul style="list-style-type: none"> • in combination with cisplatin for the treatment of non-small cell lung cancer • as a single agent for the treatment of pancreatic cancer
Duration of Treatment	Until Disease progression
Maximum Daily Dose	1,000 mg/m ²
Alternative Methods of Administration	NA

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: Based on the information provided by the Applicant Gemcitabine is soluble in water.
- Drug Product: Since this product is a parenteral solution, BCS classification is not applicable.

2. Biowaivers/Biostudies

- Biowaiver Requests: Exclusion of th (b) (4) mannitol and th (b) (4) sodium acetate, is not expected to have an impact on the disposition of gemcitabine from the Applicant's proposed formulation as compared to the reference formulation. Therefore, the sponsor's request for a waiver of the in vivo study for their proposed product is granted.
- PK studies: N/A
- IVIVC: N/A

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

<p>Application Technical Lead Signature: A complete response action is recommended due to inadequate manufacturing and facilities status and one manufacturing process deficiency.</p>	
<p>Olen Stephens, Ph.D. Acting Branch Chief OMPT/CDER/OPQ/ONDP/DNDPI/NDPBI</p>	<p align="center">Olen Stephens - S</p> <p><small>Digitally signed by Olen Stephens - S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens - S 0.9.2342.19200300.100.1.1=200558826 Date: 2015.10.29 14:59:49 -04'00'</small></p>

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

21. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Not Applicable

Applicant's Response:

Reviewer's Assessment:

The proposed drug product Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, is a sterile solution provided as a ready-to-infuse solution. Since this is a parenteral solution, in-vitro dissolution testing is NOT part of the specifications.

22. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The same formulation was used for development and the commercial product. No bridging is needed.

Gemcitabine is a nucleoside metabolic inhibitor indicated:

- 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.

Pharmaceutical Information

Listed Drug Name:	Gemzar®
Innovator Company Name:	Eli Lilly and Company
Drug Substance:	Gemcitabine hydrochloride
Strength:	(b) (4)

The Listed Drug, Gemzar[®], is a lyophilized powder of gemcitabine hydrochloride that contains mannito (b) (4). It is reconstituted in normal saline to an initial concentration of 38 mg/mL and then further diluted with 0.9% Sodium Chloride Injection and the final concentrations may be as low as 0.1

mg/mL¹. Reconstituted Gemzar® is a clear, colorless to light straw-colored solution.

The proposed Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL is a clear, colourless, sterile solution provided as a ready-to-infuse solution, supplied in ten fill volumes (1200 mg/120 mL, 1300 mg/130 mL, 1400 mg/140 mL, 1500 mg/150 mL, 1600 mg/160 mL, 1700 mg/170 mL, 1800 mg/180 mL, 1900 mg/190 mL & 2000 mg/200 mL in 200 mL infusion bag and 2200 mg/220 mL in 250 mL infusion bag). The Gemcitabine HCl in 0.9 % Sodium Chloride Injection is ready to infuse (RTI) product to be administered by the intravenous route and does not requires further dilution.

Sun's proposed product is in solution with 0.9 % Sodium Chloride, whereas the reference product is a lyophilized formulation of Gemcitabine Hydrochloride in Mannitol and Sodium Acetate, needing reconstitution followed by further dilution with 0.9 % Sodium Chloride in the infusion bag.

Gemzar® contains mannito (b) (4) and sodium acetat (b) (4) (b) (4) in the lyophilized powder whereas these inactive ingredients present in Sun's formulatio (b) (4)

There is another approved product for Gemcitabine Injection i.e. Hospira's Gemcitabine Injection, 38 mg/mL approved in NDA 200795. The comparative compositions for Sun's proposed product as well as two approved products (Gemzar® and Gemcitabine Injection, 38 mg/mL [Hospira]) are shown in Table 1 below

Table 1: A side-by-side comparison of Sun's Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, Gemzar® (Lowest Labeled Concentration (b) (4) and Undiluted) and Gemcitabine Injection, 38 mg/mL (Hospira):

¹ Label: GEMZAR http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020509s0771bl.pdf

Ingredient	Amount (mg per mL)		
	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL	Reconstituted Gemzar®	Gemcitabine Injection, 38 mg/mL (Hospira Inc.)
	10 mg/mL	(b) (4)	
Gemcitabine hydrochloride, USP	10 ¹		
Mannitol	--		
Sodium acetate	--		
Sodium chloride, USP	9		
Hydrochloric acid, NF	<i>q.s.</i> to pH 6.0 – 8.0		
Sodium hydroxide, NF			
Water for Injection, USP	<i>q.s.</i> up to 1 mL		

q.s. = Quantity sufficient

¹Gemcitabine base equivalent to 11.38 mg of Gemcitabine Hydrochloride USP.

²Following dilution for infusion

³Following initial reconstitution

The Applicant also conducted comparative testing of their proposed product (“ready-to-infuse” solution) to the listed drug, Gemzar® (lyophilized powder) reconstituted and diluted to 0.1 mg/mL (b) (4) and 38 mg/mL, and Hospira’s Gemcitabine Injection, 38 mg/mL (concentrated solution) as supplied and when diluted to 0.1 mg/mL and (b) (4) (b) (4). This comparison is provided in table 2.





Table 3: Comparison between the listed drug and proposed drug product

² <http://www.drugs.com/pro/dextrose-and-sodium-chloride-injection.html>

	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection (Sun Pharmaceutical Industries Limited)	Gemzar[®] (Gemcitabine HCl For Injection) (Lilly USA, LLC)
Conditions of Use	<ul style="list-style-type: none"> • <i>ovarian cancer</i>: in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. • <i>breast cancer</i>: 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. • <i>lung cancer</i>: in combination with cisplatin for the treatment of non-small cell lung cancer. • <i>pancreatic cancer</i>: as a single agent for the treatment of 	<ul style="list-style-type: none"> • <i>ovarian cancer</i>: in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. • <i>breast cancer</i>: 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. • <i>lung cancer</i>: in combination with cisplatin for the treatment of non-small cell lung cancer. • <i>pancreatic cancer</i>: as a single agent for the treatment of

	pancreatic cancer.	(b) (4)
Active Ingredient(s)		
Inactive Ingredient(s)		
Route of administration		
Dosage form		
Strength		

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OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

A waiver of the in vivo bioequivalence study requirement is granted.
From the Biopharmaceutics perspective, NDA 208313 for Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL is recommended for **APPROVAL**.

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Anand's assessment and approval recommendation for NDA 208313.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

23. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: see the Microbiology review under section 21.

Reviewer's Assessment: See Microbiology review under section 21.

2.3.P.7 Container/Closure System

24. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: see the Microbiology review under section 21.

Reviewer's Assessment: See Microbiology review under section 21.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

25. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: Not applicable.

Reviewer's Assessment: Not applicable.

26. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: Not applicable.

Reviewer's Assessment: Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Recommended

Helen Ngai, Ph.D.
OPQ/ OPF/ DMA/ Branch 1

Secondary Review Comments and Concurrence:

Jesse Wells, Ph.D.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

27. Is the applicant's claim for categorical exclusion acceptable?

28. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment: Sun Pharmaceuticals Industries Ltd. claimed a categorical exclusion from the requirement of an Environmental Assessment as per 21 CFR 25.31 (a).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The categorical exclusion claim is granted.
Olen Stephens, Application Technical Lead

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Comment from the ATL: Labeling review was not performed this review cycle as the clinical division opted to take action on the basis of the inadequate facilities status. The notes below may be used for initial labeling review upon resubmission of the NDA.

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

GEMCITABINE (b) (4) **injection, for intravenous use**

Initial U.S. Approval: 1996

----- **DOSAGE FORMS AND STRENGTHS** -----

Singl (b) (4); infusion bags of gemcitabin (b) (4)

- 1,200 mg in 120mL (3)
- 1,300 mg in 130mL (3)
- 1,400 mg in 140mL (3)
- 1,500 mg in 150mL (3)
- 1,600 mg in 160mL (3)
- 1,700 mg in 170mL (3)
- 1,800 mg in 180mL (3)
- 1,900 mg in 190mL (3)
- 2,000 mg in 200mL (3)
- 2,200 mg in 220mL (3)

(b) (4)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Gemcitabine (b) (4) Injection	Inadequate
Dosage form, route of administration	Injection for intravenous use	Adequate
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Provided for all strengths	Adequate

Conclusion: Edits recommended

(b) “Full Prescribing Information” Section

Singl ^{(b) (4)} infuse ba ^{(b) (4)}

- 1,200 mg gemcitabine in 0.9% sodium chloride injection (1,200 mg/120 mL)
- 1,300 mg gemcitabine in 0.9% sodium chloride injection (1,300 mg/130 mL)
- 1,400 mg gemcitabine in 0.9% sodium chloride injection (1,400 mg/140 mL)
- 1,500 mg gemcitabine in 0.9% sodium chloride injection (1,500 mg/150 mL)
- 1,600 mg gemcitabine in 0.9% sodium chloride injection (1,600 mg/160 mL)
- 1,700 mg gemcitabine in 0.9% sodium chloride injection (1,700 mg/170 mL)
- 1,800 mg gemcitabine in 0.9% sodium chloride injection (1,800 mg/180 mL)
- 1,900 mg gemcitabine in 0.9% sodium chloride injection (1,900 mg/190 mL)
- 2,000 mg gemcitabine in 0.9% sodium chloride injection (2,000 mg/200 mL)
- 2,200 mg gemcitabine in 0.9% sodium chloride injection (2,200 mg/220 mL)

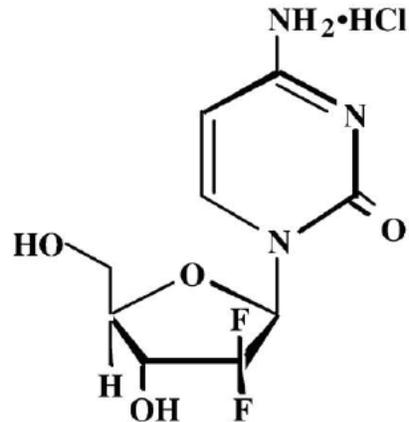
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Provided	Adequate
Strengths: in metric system	Yes, complies	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Described as a ready to infuse bag. Individual labels are not described here.	Adequate

Conclusion: Edits recommended

#11: Description (21CFR 201.57(c)(12))

Gemcitabine ^{(b) (4)} is a nucleoside metabolic inhibito ^{(b) (4)} Gemcitabine hydrochloride is 2’-deoxy-2’,2’-difluorocytidine monohydrochloride (β-isomer ^{(b) (4)}



The ^{(b) (4)} formula for gemcitabine hydrochloride is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine hydrochloride is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine ^{(b) (4)} in sodium chloride injection is a clear, colorless, sterile solution that is ^{(b) (4)} in single-dos ^{(b) (4)} infuse bag ^{(b) (4)}

Each 100 mL ^{(b) (4)} contains 1,000 mg of gemcitabine ^{(b) (4)} ^{(b) (4)} 900 mg of sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. **Include a salt equivalence statement**

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Gemcitabine Injection	Inadequate; see revisions above
Dosage form and route of administration	Solution for Injection for infusion	
Active moiety expression of strength with equivalence statement for salt (if applicable)	Equivalence statement not included	Edits to sponsor
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided quantitatively	Adequate
Statement of being sterile (if applicable)	Yes	Adequate
Pharmacological/ therapeutic class	Nucleoside metabolic inhibitor	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Solubility provided	Adequate

Conclusion: Comment to the applicant:

1. The product should be referred to as a single-dose product.
2. Include an equivalence statement with regard to the amount of hydrochloride salt per free base.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Gemcitabine ^{(b) (4)} in sodium chloride injection is a clear, colorless, sterile solution in a single-dose ^{(b) (4)} infuse bag with an aluminum overwrap. The container closure is not made with natural latex. It is available in ^{(b) (4)} presentations:

Strength	Package	NDC number
1,200 mg in 120mL	1 single dos ^{(b) (4)} bag per carton	62756-073-60
1,300 mg in 130mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,400 mg in 140mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,500 mg in 150mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,600 mg in 160mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,700 mg in 170mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,800 mg in 180mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
1,900 mg in 190mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
2,000 mg in 200mL	1 single dos ^{(b) (4)} bag per carton	62756 ^{(b) (4)} -60
2,200 mg in 220mL	1 single dos ^{(b) (4)} bag per carton	62756-974-60

16.2 Storage and Handling

Unopened infusion bags of (b) (4) are stable until the expiration date indicated on the package when stored at 25°C (77°F) (b) (4) excursions between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature] [see *Dosage and Administration (2.6)*]. **Do not freeze** (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Provided	adequate
Available units (e.g., bottles of 100 tablets)	provided	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	provided	adequate
Special handling (e.g., protect from light, do not freeze)	Comment to the applicant	inadequate
Storage conditions	provided	adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512 Manufacture by: Sun Pharmaceutical Ind. Ltd. Halol-Baroda Highway, Halol-389 350, Gujarat, India	Adequate

Conclusion: Comments for the applicant:

1. Include instructions to not freeze the product.
2. The product should be labeled as a "single-dose" product.
3. Cytotoxic disposal statement should be included

2. Container and Carton Labeling

- 1) **Immediate Container Label – note that only a representative label for one strength is copied below. Labels for all strengths are provided in the NDA.**

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Gemcitabin injection (b) (4)	Inadequate; see edits
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expressed in terms of total amount in infusion bag on a free base basis of gemcitabine; Applicant should highlight equivalence statement	Comment to applicant
Route of administration 21.CFR 201.100(b)(3))	For intravenous use only	Adequate
Net contents* (21 CFR 201.51(a))	Provided	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided	Adequate
Lot number per 21 CFR 201.18	Provided	Adequate
Expiration date per 21 CFR 201.17	Listed	Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Listed as Sun Pharmaceutical Ind. Ltd.	Adequate
Others	“Sun Pharma” promotional material may need to be removed, but we defer to DMEPA	Adequate

Conclusion: Comments for the applicant:
 1. Include an equivalence statement highlighting dosing based on free base of gemcitabine.

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Gemcitabin injection (b) (4)	Inadequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Listed	Adequate
Net contents (21 CFR 201.51(a))	Listed	Adequate
Lot number per 21 CFR 201.18	Space provided	Adequate
Expiration date per 21 CFR 201.17	Space provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Listed quantitatively	Adequate
Sterility Information (if applicable)	Labeled as Sterile	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Labeled Rx	Adequate
Storage Conditions	Listed as USP Controlled Room Temp.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Statement is provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not listed, but product is Rx only	Adequate
Route of Administration (not	Listed as for Intravenous Use Only	Adequate

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		
Other	Include a equivalence statement to make it clear dosing is based on the gemcitabine free base	Inadequate
(b) (4) symbols	h (b) (4) symbols for all container closure labels should be remove (b) (4)	Inadquate

Conclusion: Comment for the applicant:

1. Include an equivalence statement to make it clear dosing is based on the gemcitabine free base.
2. Remov (b) (4) symbols for all container closure label (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Olen Stephens, Application Technical Lead

II. List of Deficiencies To Be Communicated

III. Attachments

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	Initial Risk Ranking	Final Risk Ranking	Lifecycle Considerations
Sterility	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Non-sterile unit(s) 	High	High	<p>The produc (b) (4)</p> <p>This remains a critical unit operation</p>
Endotoxin Pyrogen	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Excessive Endotoxin Levels 	32	Medium	
Assay (API), stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Impurity formation due to (b) (4) • Organic solvents 	Low	Low	
Uniformity of Dose (Fill Volume/deliverable volume)	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Insufficient dose 	Low	Low	This remains a fill from a bulk solution that appears stable over the proposed hold times.
Osmolality	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation • Edema 	Low	Low	

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	Initial Risk Ranking	Final Risk Ranking	Lifecycle Considerations
pH- (Low)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation 	Low	Low	
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Irritation • Embolism 	Medium	Medium	(b) (4)
Leachable extractables	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Generation of impurities 	Low	Low	
Appearance (Color/turbidity)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Degradation 	Low	Low	