

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022534Orig1s000**

**CHEMISTRY REVIEW(S)**

**OFFICE OF NEW DRUG AND QUALITY ASSESSMENT  
CDER/FDA**

**PRE-MARKETING CMC ASSESSMENT**

NDA: 22534  
Original NDA Submission: 21-Apr-2009  
Applicant: Sun Pharma  
Product: Docefrez™ (Docetaxel) for Injection  
Document Reviewed: SD 0021; 03-Nov-2010  
SD 0022; 21-Dec-2010  
Primary Reviewer: Debasis Ghosh, M. Pharm., Ph.D.  
Date of Review: 24-Mar-2011  
Review: #2

**Summary:**

- The applicant (Sun Pharma) submitted an NDA on 21-Apr-2010 under 505(b)(2) to commercialize Docefrez™ (docetaxel) for Injection 20 mg/vial and 80 mg/vial and Diluents for the 20 mg and 80 mg vials.
- On 17-Feb-2010, the CMC recommended approval (Review #1) of this NDA. The shelf life of the product is recommended for (b)(4) when stored at 2°C-8°C (36°F-46°F) and protected from light.
- Sun Pharma received tentative approval under 21 CFR 314.105 on 23-Feb-2010. Final approval is pending.

In an Amendment (SR 020) submitted on 03-Nov-2010, Sun Pharma provided update on the stability data for Docefrez (docetaxel) for Injection, 20 mg/vial and 80 mg/vial and Diluent for 20 mg and 80 mg strength.

In addition, Sun Pharma proposed the following changes:

1. Intended commercial batches (b)(4) with respect to the exhibit batches (exhibit batches were originally submitted in the initial NDA).



Considering the importance and nature of the proposed changes, the Agency categorized the above changes as Class 2 Response and conveyed this decision to Sun Pharma on 24-Nov-2010. New PDUFA date is May 3, 2011.

In an Amendment (SD022) submitted on 21-Dec-2010, Sun Pharma proposed to withdraw following changes previously submitted as Amendment SD 021:

In this Amendment (SD022), Sun Pharma proposed additional changes:

- (1) Revised intended batch manufacturing record for drug product and diluent with changes described are provided in *Section 3.2.P.3.3*
- (2) Media fill simulation studies have been performed for the new equipments, summary report for these media fills, growth promotion results and environmental monitoring data are provided in *Section 3.2.P.3.5*. Comparative summary of media fill parameters and process parameters are also provided in *Section 3.2.P.3.5*.

**Recommendation and Conclusion:**

- **From CMC perspective the submission is acceptable and is recommended for approval, pending satisfactory resolution of labeling issues.**
- **Based on the updated stability data, a 30-month expiration dating period is granted for the packaged drug product when stored at 2°C to 8°C (36°F to 46°F) and protected from light.**

## CMC Review Notes

Here is the summary of 'acceptable' CMC changes:

(1) Based on the information provided for the proposed commercial batches for 20 mg Docefrez and Diluent for 20 mg Docefrez, the (b) (4) is acceptable.

(2) Based on drug product stability data, **30 months** expiration dating period is granted for drug product (Docefrez 20 mg/vial and 80 mg/vial) and Diluent (for Docefrez 20 mg and for Docefrez 80 mg) when stored at 2°C to 8°C (36°F to 46°F) protected from light.

### Updated Product Stability information

#### CMC Information Contained in SD 021:

Docetaxel Vials:

- Sun Pharma provided accelerated stability ( $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ ) data from 3 batches each for 20 mg and 80 mg vials containing docetaxel lyophilized powder. The results from all 6 batches showed no significant change of any of the stability indicating attributes during 6 months period.
- Sun Pharma updated Long-term ( $5 \pm 3^\circ\text{C}$ ) stability data for 36 months for two 80 mg vials and one 20 mg vial. The data showed no significant change of any stability indicating attributes.
- Sun Pharma updated long-term ( $5 \pm 3^\circ\text{C}$ ) stability data for 24 months for one 80 mg vial and two 20 mg vials showed no significant change of any stability indicating attributes.

Evaluation: Satisfactory

All batches met the specification for the quality attributes.

Essentially, the data from accelerated stability ( $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ ) for 6 months and long-term stability ( $5 \pm 3^\circ\text{C}$ ) for 24 months from three batches each for 20 mg and 80 mg strengths showed no significant changes of the stability indicating attributes. Based on the principles of ICHQ1E, a shelf-life of (b) (4) is granted.

Diluent Vials:

- Sun Pharma provided accelerated ( $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ ) stability data for six diluent vials (three each diluent for 80 mg and 20 mg vials). The results form 6 months stability data showed no significant change of quality attributes after 6 months.
- Sun Pharma provided 36 months long-term ( $5 \pm 3^\circ\text{C}$ ) stability data from two 80 mg diluent vials and from one 20 mg diluent vial. The data showed no significant change of quality attributes.
- Sun Pharma provided 24 months long-term ( $5 \pm 3^\circ\text{C}$ ) stability data from one 80 mg diluent and two 20 mg diluent vials. The data showed no significant change of quality attributes.

Evaluation: Satisfactory

All batches met the specification for the quality attributes.

Essentially, the data from accelerated stability ( $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$ ) for 6 months and long-term stability ( $5 \pm 3^\circ\text{C}$ ) for 24 months from three diluent batches each for 20 mg and 80 mg strengths showed no significant changes of the stability indicating attributes. Based on the principles of ICHQ1E, a shelf-life of (b) (4) may be granted.

### Updated Information for Commercial Batch

The applicant provided following updated information as an Amendment (SD 0021) to NDA 22534.

Product/Diluent		Exhibit batch size / Intended batch size submitted in tentatively approved NDA	Intended batch size for commercial batches (b) (4)
Docefrez™ for Injection,	20 mg/vial		
	80 mg/vial		
Diluent for Docefrez™ for Injection	20 mg/vial		
	80 mg/vial		

Recently (Amendment 022), (b) (4) was withdrawn. In this amendment, new Executed Master Batch Record was provided. Since it is a pre-approval submission, the updated information will be considered as an amendment to NDA 22534 for the assessment of the intended commercial batch size.

Evaluation: Satisfactory

- It has been noted that the updated information is provided as pre-approval submission (Amendment to NDA). While this NDA received tentative approval status from the Agency on 23-Feb-2010, the new information will not be considered as post-approval changes. Because of the importance of the proposed changes (SD 021 and SD 022), the Agency classified this submission as Class 2.
- In the original submission, the applicant provided following information in the Master Batch Record:

Product	Batch Number	Batch Size (b) (4)	Stability Study	Comment
Docefrez 20 mg/vial	JK70373		6 months accelerated; 24 months long-term; ongoing	Satisfactory.
Docefrez 80 mg/vial	JK61019		6 months accelerated; 36 months long-term;*	Satisfactory
Diluent for 20 mg/vial	JK70446		6 months accelerated; 24 months long-term; ongoing	Satisfactory

Product	Batch Number	Batch Size	Stability Study	Comment
Diluent for 80 mg/vial	JK70330	(b) (4)	6 months accelerated; 36 months long-term;*	Satisfactory

\*updated SD021 Nov 3, 2010

- In the Amendment SD 022, the applicant provided following information in the Master Batch Record:

Product	Batch Number	Batch Size	Stability Study	Comment
Docefrez 20 mg/vial	JKJ4384	(b) (4)	ongoing	This batch size is considered as intended commercial batch size.
Docefrez 80 mg/vial	(b) (4)	(b) (4)	ongoing	The batch size is same as previous batch. This batch size is considered as the intended commercial batch.
Diluent for 20 mg/vial	JKJ3894	(b) (4)	ongoing	This batch size is considered as intended commercial batch size.
Diluent for 80 mg/vial	JKJ4434	(b) (4)	ongoing	The batch size is same as previous batch. This batch size is considered as the intended commercial batch.

- In summary, the intended commercial batch size for
  - 20 mg/vial is (b) (4)
  - 80 mg/vial is (b) (4)
  - Diluent for 20 mg/vial is (b) (4)
  - Diluent for 80 mg/vial is (b) (4)
 are acceptable.

#### Updated equipment for drug product and diluent vial

The applicant updated a list of equipments for the microbiological process. The new information for the equipments to be used (b) (4) has been reviewed by Microbiology reviewer. It has been noted that the (b) (4) was withdrawn.

#### Evaluation:

This update is related to microbiology issues. No CMC issues to address. On 01-Mar-2011, Microbiology reviewer (John Metcalf) recommended 'approval' of this NDA.

(b) (4) **Docetaxel for Injection 20 mg/vial**  
In Amendment SD022, the applicant decided to withdraw (b) (4) procedure.

**Overall Evaluation: Satisfactory.**

*CMC recommends approval pending satisfactory resolution of labeling changes.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEBASIS GHOSH  
03/24/2011

SARAH P MIKSINSKI  
04/05/2011

**NDA 22-534**

**DOCEFREZ™ INJECTION**

**Sun Pharma**

**Debasis Ghosh, M. Pharm., Ph.D.  
Review Chemist**

**Office of New Drug Quality Assessment  
Division of Pre-marketing Assessment and Manufacturing Science  
Branch V**

**CMC REVIEW OF NDA 22-534  
For the Division of Drug Oncology Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 22-534
2. REVIEW #: 1
3. REVIEW DATE: 16-FEB-2010
4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	21-APR-2009
Amendment SD 0006	20-AUG-2009
Amendment SD 0007	21-AUG-2009
Amendment SD 0011	28-DEC-2009
Amendment SD 0012	04-JAN-2010
Amendment SD 0013	07-JAN-2010
Amendment SD 0014	02-FEB-2010

7. NAME & ADDRESS OF APPLICANT:

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Fax: 301-652-6739

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Docefrez™ Injection
- b) Non-Proprietary Name: Docetaxel Injection
- c) Code Name/# (ONDQA only): NA

## CMC Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

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

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)\*, the RLD is Taxotere® (docetaxel) for Injection, 20 mg and 80 mg vials, Sanofi-Aventis, NDA (b) (4)

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 20 mg vial (20 mg/0.8 mL); 80 mg vial (24 mg/mL)

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

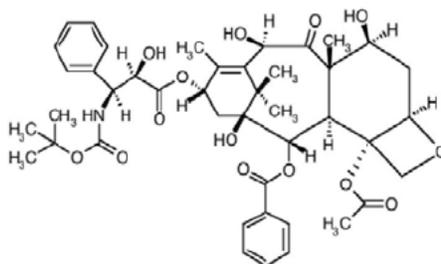
SPOTS product – Form Completed

Not a SPOTS product

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

**Chemical Name:** (2R,3S)-N-Carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5 $\beta$ -20-epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

**Structural Formula of Docetaxel**



Molecular Formula: C<sub>43</sub>H<sub>53</sub>NO<sub>14</sub>

Molecular Weight: 807.88

\* see 505(b)(2) assessment in DARRTS (02/01/2010)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	20-OCT-2009	Reviewed by Debasis Ghosh
	III			1	Adequate	17-NOV-2009	Reviewed by Debasis Ghosh
	III			4	N/A	N/A	See CMC review Sec P.7

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**B. Other Documents: N/A**

## CMC Review Data Sheet

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	05-JUN-2009	Office of Compliance
Pharm/Tox	Pending		Margaret Brower
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA*	Pending		Loretta Holmes
EA	Categorical exclusion (see review)		
Microbiology	Approval	13-NOV-2009	John W Metcalf

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 22534

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved.

The proposed shelf-life of (b) (4) (when stored between 2°C-8°C (36°F-46°F), protected from bright light) is acceptable.

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

None

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

Drug substance, docetaxel, is a white-to-off-white powder, insoluble in water and freely soluble in ethanol. It is hygroscopic and may exhibit (b) (4) possible polymorphic forms. Since the final reconstituted drug product is a solution, the polymorphic form has no influence on the efficacy or safety of the drug product.

The anhydrous form of docetaxel has been used for this drug product formulation. It should be noted that the RLD drug substance is a trihydrate species (CAS # 148408-66-6) whereas the proposed drug substance is an anhydrous species (CAS # 11497-28-5).

Structurally, docetaxel has eleven chiral centers and many stereoisomers are possible. (b) (4)

The physicochemical properties including hygroscopicity, chirality, solubility, polymorphism and pH sensitivity are important in regard to the manufacturing process and stability of drug product.

Since drug substance may absorb moisture from the environment due to its hygroscopic nature, it is stored in (b) (4) bags

## Executive Summary Section

placed in (b) (4) bottles and stored (b) (4) with adequate protection of light and moisture.

The manufacturing process of the drug substance has been provided in DMF (b) (4). According to the applicant, the manufacturer has established a (b) (4) retest period for the drug substance.

**(2) Drug Product**

The proposed drug product, Docefrez™ Injection, is supplied as a two-part product. One part is a sterile, lyophilized powder supplied in a (b) (4) glass vial containing either 20 mg or 80 mg of anhydrous Docetaxel. The other part is an accompanying sterile, non-pyrogenic, diluent vial containing ethanol, USP (35.4% w/w) and polysorbate 80, NF (b) (4). The contents of the two vials are intended for reconstitution and further dilution with 250 mL isotonic 5% dextrose or normal saline before administration by intravenous infusion.

The proposed drug product is pharmaceutically equivalent to the Reference Listed Drug (RLD), Taxotere® (docetaxel) Injection Concentrate (NDA 20449), marketed by Sanofi Aventis. Except the amount of ethanol, it contains the same active and inactive ingredients (b) (4) as RLD's but differ in dosage form. In RLD, the active vial contains drug substance in polysorbate 80 and diluent vial contains 13% w/w ethanol in water for injection. In the proposed drug product, active vial contains drug substance in the form of lyophilized powder and diluent vial contains (b) (4) ethanol in polysorbate 80. It has been noted that the amount of ethanol in the proposed formulation is higher than RLD formulation. It is, however, well within the permissible limits of Inactive Ingredient Guide (IIG) of FDA for intravenous infusion. The amount of polysorbate 80 is (b) (4).

The proposed drug product, Docefrez™ Injection, will be marketed as co-packaged vials. Each package contains one active ingredient vial containing 20 mg or 80 mg lyophilized powder of docetaxel and one diluent vial containing 1 mL or 4 mL solution of ethanol (35.4% w/w) in polysorbate 80. The RLD contains 20 mg or 80 mg of drug formulated in 0.5 mL or 2 mL of polysorbate 80, respectively. RLD's docetaxel concentrate should be diluted with the supplied diluent (13% ethanol in water) before adding to 5% Dextrose or normal saline solution for IV infusion. Two-step dilution process is required for both RLD and the proposed product. The active ingredient in the proposed drug product is supplied as a sterile, lyophilized powder rather than as a concentrated solution as described in RLD. In case of RLD, the concentrated solution should be diluted with the diluent to achieve a concentration of 10 mg/mL whereas the concentration of the proposed reconstituted solution would be 24 mg/mL.

## Executive Summary Section

The applicant proposed a formulation which is similar to the currently marketed product but differ in dosage forms. The applicant submitted a biowaiver under 21 CFR 320.22(b)(1). From the bioequivalence perspective, docetaxel (the active ingredient) and polysorbate 80 amount would be (b) (4) after reconstitution with the diluent. The amount of ethanol would be higher in the proposed formulation (35.4%) compared to RLD (13% w/w). However, the amount of ethanol in the proposed formulation is lower than IIG limits of ethanol in parenteral solution.

The proposed drug product is manufactured by (b) (4). The drug product obtained by this process is a white mass in a colorless glass vial. The proposed diluent is prepared by mixing ethanol and polysorbate 80 (b) (4).

The drug product active vial containing lyophilized docetaxel is packaged in a (b) (4) (for 20 mg) or (b) (4) (for 80 mg) clear colorless Type I glass vials with rubber stopper and flip-off aluminum seal. The drug product diluent vials (both for 20 mg and 80 mg) containing ethanol in polysorbate 80 are packaged in (b) (4) Type I clear glass vials. Both active vial and diluent vial are color coded with aluminum flip-off tops and securely co-packaged in a molded frame.

The specification for drug product active vial include description, identification, (b) (4), reconstitution time, constituted solution, assay of docetaxel, percent transmittance at (b) (4) absorbance at (b) (4), impurities, microbiological evaluations. The specification for diluent for docetaxel for injection include identification, content of ethanol and microbiological evaluation. In the original submission, it was noted that the specification for related substances and assay of docetaxel in drug product active vial at release were (b) (4). Ethanol content at release and during shelf-life was (b) (4). In a recent communication (28-DEC-2009), the applicant agreed to harmonize the specifications. Based on the information submitted on 04-JAN-2010, the specification was updated to reflect those changes.

The applicant reported (b) (4). All impurities are found to be below the qualification threshold level as per ICHQ3B. (b) (4)

The applicant provided information to qualify this impurity (see Pharmacology Toxicology Review by Margaret Brower) (b) (4). The applicant also provided the batch analysis data for all three registration batches for active vials (20 mg and 80 mg)

## Executive Summary Section

and diluent vials. Microbiology attributes have been reviewed by John Metcalf (see Microbiology Review) and found to be satisfactory.

The proposed formulation should be stored between 2°-8°C protected from light and moisture. Based on the real-time long-term and accelerated stability data, (b) (4) expiration period may be granted.

The proposed proprietary name 'Docefrez' was approved by DMEPA on 11-AUG-2009 (see communication in DARRTS from Carol Holquist).

The applicant proposed a co-packaged product containing active vial (lyophilized powder of drug substance only) and diluent vial (35.4%w/w ethanol in polysorbate 80) for two different strengths (20 mg and 80 mg). Based on the manufacturing record, the actual content of docetaxel (anhydrous) in 20 mg active vial is (b) (4) accounting for (b) (4) overfill and in 80 mg vial is (b) (4) accounting for (b) (4) overfill consistent with the overfill amount present in RLD. For the reconstitution, exactly 1 mL and 4 mL of diluents (supplied) should be added to 20 mg and 80 mg active vials, respectively. The resultant concentration in 20 mg vial and 80 mg vial after reconstitution with the diluent would be (b) (4) mg/mL and (b) (4) mg/mL, respectively. The applicant proposed that (b) (4) of reconstituted solution in 20 mg vial is equivalent to 20 mg of docetaxel whereas (b) (4) of reconstituted solution in 80 mg vial is equivalent to 80 mg of docetaxel. An internal discussion with the Review Team was conducted to finalize the carton and vial labels for both active and diluent vials. Following FDA's suggestion, the applicant provided revised information for the extractable amount of the reconstituted solution in carton and vial labels. Based on the Amendment SD 14 (12-Feb-2010), 0.8 mL from 20 mg vial and (b) (4) from 80 mg vial of the reconstituted solution would be equivalent to 20 mg and 80 mg of docetaxel, respectively. After mixing the reconstituted solution with the intravenous solution (250 mL), the amount of polysorbate 80 in the final admixture in the proposed formulation would be (b) (4).

Pursuant to 21 CFR 314.55( c)(2)(ii), the applicant requested a waiver of pediatric assessment of docetaxel for Injection.

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

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour (b) (4). The proposed indications are for Breast Cancer, Non-Small Cell Lung Cancer, Prostate Cancer (b) (4).

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

The NDA can be approved from a CMC perspective. There are no outstanding CMC deficiencies.

## Executive Summary Section

**III. Administrative**

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary.

**A. Reviewer's Signature:**

*(See appended electronic signature page)*

Debasis Ghosh, M. Pharm., Ph.D., Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch V, Division III, ONDQA

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22534	ORIG-1	SUN PHARMA GLOBAL FZE	DOCEFREZ INJECTION (20/80 MG/VIAL)

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/s/

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DEBASIS GHOSH  
02/17/2010

Sarah Pope Miksinski  
02/17/2010

**Initial Quality Assessment  
Branch V  
Pre-Marketing Assessment Division III  
Office of New Drug Quality Assessment**

**OND Division:** Division of Drug Oncology Products  
**NDA:** 22-534  
**Applicant:** Sun Pharma Global FZE.  
**Letter Date:** 23 April, 2009  
**Stamp Date:** 23 April, 2009  
**PDUFA Goal Date:** 23 February, 2009 (standard)  
**Trade name:** Docefrez  
**Established Name:** Docetaxel  
**Dosage Form/Strength:** Lyophilized powder for Injection - 20 mg/ vial and 80 mg/vial  
**Route of Administration:** IV  
**Indication:** Breast cancer, non-small cell lung cancer, prostate cancer (b) (4)

**Regulatory Filing Related IND/DMF** For 505 (b) (2) (b) (4)

**Assessed by:** Haripada Sarker

Yes No

**ONDQA Fileability:** x

**Comments for 74-Day Letter:** x

**Background Summary**

The application introduces the drug product, Docetaxel Injection by Sun Pharma. The proposed drug product, Docetaxel Injection (Docefrez), is packaged in two packaging presentations, each consisting of the following: (a) a single use drug product vial containing docetaxel lyophilized powder (20 mg or 80 mg, amounts expressed in base equivalents) (b) a single use diluent vial containing 35.4% w/w ethanol in polysorbate 80. Sun Pharma's Docetaxel for Injection is proposed for the treatment of breast cancer, non-small cell lung cancer, prostate cancer (b) (4) approved indications for the reference listed drug (RLD).

The RLD, Docetaxel (Taxotere) injection by Sanofi Aventis was previously approved by the agency under NDA 20-449 (May 14, 1996), for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. It is noted that Taxotere® under NDA 20-449 is a solution

formulation (40mg base/mL), which is reconstituted with sterile WFI, USP. In the case of Sun Pharma's Docetaxel, the drug is formulated as a lyophilized powder, which is initially diluted with a different excipient, 35.4% w/w ethanol in polysorbate 80. The contents of the two vials are intended for reconstitution and further dilution in 5% dextrose or 0.9% sodium chloride prior to administration by intravenous infusion.

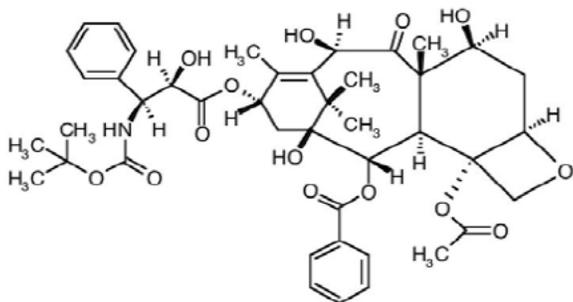
A pre-NDA meeting was held on July 2, 2008. The major CMC issue was related to level of one drug substance impurity (b) (4). Sun Pharma has requested the qualification of impurity (b) (4) in the drug substance. Rest of the drug substance impurities at release are controlled at or below ICHQ3A. The CMC information of the NDA is submitted as per CTDQ format.

### Drug Substance (DS)

(b) (4) manufactures docetaxel on behalf of Sun Pharma Global FZE (Sun Pharma), under current Good Manufacturing Practices (cGMP) as the anhydrous, non-pyrogenic powder for use in the drug product described above. The applicant referred to (b) (4) for drug substance and provided a Letter of Authorization.

In the NDA submission, the applicant provided brief drug substance information regarding identity, physico-chemical properties and specifications. Docetaxel is an optically active compound. It is a semi-synthetic drug substance made from its natural precursor 10-deacetylbaccatin III. Docetaxel is highly lipophilic and practically insoluble in water. As the structural formula of docetaxel has multiple stereogenic centers, many isomers are theoretically possible. However, docetaxel drug substance in solid form is very stable. (b) (4)

(b) (4) Specifications and the test data on four batches of docetaxel drug substance (batch 70745AR002, batch 70745AR003, batch 70745AA015 and batch 70745AR009) have been provided. The drug substance is identified with following structure.



The stability of the docetaxel drug substance is monitored by (b) (4). Details are cross-referenced to the DMF. Currently, the supplier has established and recommended a (b) (4) retest period for the drug substance based on the available stability data when stored (b) (4)

and protected from light. An EES request was submitted to the Office of Compliance for the proposed sites provided in the May 10, 2009 amendment.

The proposed drug substance manufacturing site is listed below:



*Drug Substance Critical Issues*

- Justification of (b)(4).
- In solution, docetaxel is known to undergo pH assisted epimerization, leading to the formation of variety of isomers. Impurities including the degradation product(s) of docetaxel should be evaluated and need to be qualified by appropriate justification. Interaction with Pharmacology/Toxicology may be needed for this assessment.
- (b)(4) is the new drug substance manufacturer of Docetaxel from (b)(4). The cross-referred DMF (b)(4) should be evaluated to support the NDA.
- EER information for drug substance needs to be re-examined for accuracy.

**Drug Product (DP)**

The proposed drug product is presented as a two-part product. One part is a sterile, lyophilized, non-pyrogenic powder supplied in (b)(4) glass vials containing either 20 mg or 80 mg of the anhydrous docetaxel active ingredient. The other part is an accompanying diluent vial containing ethanol, USP (35.4% w/w) and polysorbate 80, NF (b)(4). The contents of the two vials are intended to be reconstituted and further diluted in 5% dextrose or 0.9% sodium chloride before administration by intravenous infusion. Following table represents the DP components and composition.

**Presentations and Composition of Docetaxel for Injection**

Component	Weight/Vial	Fill Volume*	% Composition	Function
<b>Docetaxel, 80 mg/vial</b>				
<b>Active Vial</b> (b) (4) Docetaxel	80 mg	--	100%	API
<b>Diluent Vial</b> (b) (4) Ethanol, USP Polysorbate 80, NF	(b) (4)	4.0 mL	35.4% w/w (b) (4)	(b) (4)
<b>Docetaxel, 20 mg/vial</b>				
<b>Active Vial</b> (b) (4) Docetaxel	20 mg	--	100%	API
<b>Diluent Vial</b> (b) (4) Ethanol, USP Polysorbate 80, NF	(b) (4)	1.0 mL	35.4% w/w (b) (4)	(b) (4)

API = Active Pharmaceutical Ingredient  
 \*Overages are discussed in see Section 3.2.P.2.2.2.

A comparative composition between the RLD and the DP of this submission is provided. Sun Pharma developed a docetaxel for injection product that contains the same active and inactive ingredients (b) (4) as the RLD but differs in dosage form.

Applicant utilizes the experiences with RLD to develop Docetaxel injection for this submission. (b) (4)

The proposed DP manufacturing site is listed below:

Sun Pharmaceutical Industries Limited  
 Halol-Baroda Highway, Halol – 389350  
 Gujarat, India

Following are the container/closure system and the suppliers to be used for the finished DP.

Component	Supplier	DMF # and LOA
(b) (4)		

Not applicable

Two different acceptance criteria for DP impurities assay are proposed for release and for stability specification as in the following table.

Degradation Products	DP Release Limits	DP Stability Limits
Related substances <sup>4</sup> (HPLC)		(b) (4)
Assay of docetaxel (HPLC)		

Side-by-side comparison of several DP batches from Docefrez™ and RLD (Taxotere® ) have been provided up to 18 months in stability studies. The results suggest that all the known and unknown impurities of Docefrez™ (age of 24 months/ 18 months / 12 months at 2-8°C) are comparable to Taxotere® (available age) and also within the ICH limits (b) (4) where variable levels are observed in Docefrez™ compared to Taxotere®.

Three registration batches of each strength of docetaxel for injection and the accompanying diluents have been placed on stability according to the conditions, long-term (5 ± 3°C) and accelerated (25 ± 2°C/60 ± 5% RH), summarized in following Tables.

#### Stability Protocol Summary for Active Product Batches

Storage Conditions	Sampling Time (months)									
	0	1	2	3	6	9	12	18	24	36
25 ± 2°C/60 ± 5% RH	X	Y	Y	Z	X	-	-	-	-	-
15 ± 3°C	X	-	-	Y	Z	Y	X	-	-	-
5 ± 3°C	X	-	-	Y	Y	Y	X	Y	X	X

X = Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay, particulate matter, sterility, bacterial endotoxins.

Y= Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay

Z= Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay, particulate matter

#### Stability Protocol Summary for Diluent Batches

Storage Conditions	Sampling Time (months)									
	0	1	2	3	6	9	12	18	24	36
25 ± 2°C/60 ± 5% RH	X	Y	Y	Z	X	-	-	-	-	-
15 ± 3°C	X	-	-	Y	Z	Y	X	-	-	-
5 ± 3°C	X	-	-	Y	Y	Y	X	Y	Y	X

X = Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol, particulate matter, sterility, bacterial endotoxins.

Y= Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol.

Z = Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol, particulate matter.

At present, 18-month long-term stability results are available for one batch of each strength and a 12-month long-term stability results are available for two batches of each strength. Six months of accelerated stability results are also available for each registration batch. Sun Pharma's stability protocol for the on-going ICH stability studies extends through the 36-month long-term time point and the 6-month accelerated time point.

No statistical analysis is included to support the proposed DP expiration dating. Applicant indicated to update the stability data as available. The Applicant proposes a (b) (4) expiration dating period for the Docetaxel for injection, when stored at long-term condition ( $5 \pm 3^{\circ}\text{C}$ ).

*Drug Product Critical Issues*

- New degradants in DP finished dosage form (lyophilized powder) and infusion solution, when compared with RLD batches.
- Check EES of DP sites for accuracy.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Two different acceptance criteria for DP impurities are proposed for release and for stability specification. Specifications need to be harmonized.
- Justification of (b) (4) expiration based on available stability data and whether ICH Q1E can be applied for this extrapolation.
- The DP labeling, which is submitted in PRL format, need to be evaluated for its relevant CMC sections.

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		

15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMEPA/ODS <b>EER</b>
		√		
		√		
		√		

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

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

**Comments and Recommendations**

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker  
Pharmaceutical Assessment Lead (PAL)

June 17, 2009  
Date

Sarah Pope, Ph.D.  
Branch Chief

June 17, 2009  
Date

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/s/

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Haripada Sarker  
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Sarah Pope  
7/9/2009 03:57:21 PM  
CHEMIST

**Initial Quality Assessment  
Branch V  
Pre-Marketing Assessment Division III  
Office of New Drug Quality Assessment**

**OND Division:** Division of Drug Oncology Products  
**NDA:** 22-534  
**Applicant:** Sun Pharma Global FZE.  
**Letter Date:** 23 April, 2009  
**Stamp Date:** 23 April, 2009  
**PDUFA Goal Date:** 23 February, 2009 (standard)  
**Trade name:** Docefrez  
**Established Name:** Docetaxel  
**Dosage Form/Strength:** Lyophilized powder for Injection - 20 mg/ vial and 80 mg/vial  
**Route of Administration:** IV  
**Indication:** Breast cancer, non-small cell lung cancer, prostate cancer (b) (4)

**Regulatory Filing Related IND/DMF** For 505 (b) (2) (b) (4)

**Assessed by:** Haripada Sarker

Yes No

**ONDQA Fileability:** x

**Comments for 74-Day Letter:** x

**Background Summary**

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The RLD, Docetaxel (Taxotere) injection by Sanofi Aventis was previously approved by the agency under NDA 20-449 (May 14, 1996), for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. It is noted that Taxotere® under NDA 20-449 is a solution

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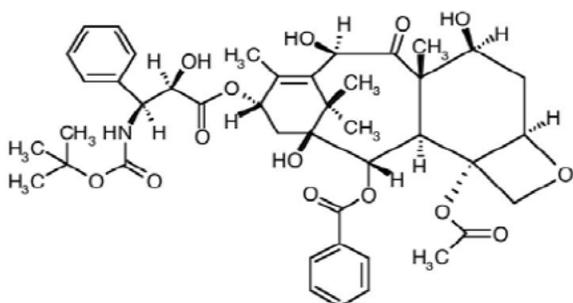
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In the NDA submission, the applicant provided brief drug substance information regarding identity, physico-chemical properties and specifications. Docetaxel is an optically active compound. It is a semi-synthetic drug substance made from its natural precursor 10-deacetylbaccatin III. Docetaxel is highly lipophilic and practically insoluble in water. As the structural formula of docetaxel has multiple stereogenic centers, many isomers are theoretically possible. However, docetaxel drug substance in solid form is very stable. (b) (4)

(b) (4) Specifications and the test data on four batches of docetaxel drug substance (batch 70745AR002, batch 70745AR003, batch 70745AA015 and batch 70745AR009) have been provided. The drug substance is identified with following structure.



and protected from light. An EES request was submitted to the Office of Compliance for the proposed sites provided in the May 10, 2009 amendment.

The proposed drug substance manufacturing site is listed below:



*Drug Substance Critical Issues*

- Justification of (b) (4).
- In solution, docetaxel is known to undergo pH assisted epimerization, leading to the formation of variety of isomers. Impurities including the degradation product(s) of docetaxel should be evaluated and need to be qualified by appropriate justification. Interaction with Pharmacology/Toxicology may be needed for this assessment.
- (b) (4) is the new drug substance manufacturer of Docetaxel from (b) (4). The cross-referred DMF (b) (4) should be evaluated to support the NDA.
- EER information for drug substance needs to be re-examined for accuracy.

**Drug Product (DP)**

The proposed drug product is presented as a two-part product. One part is a sterile, lyophilized, non-pyrogenic powder supplied in (b) (4) glass vials containing either 20 mg or 80 mg of the anhydrous docetaxel active ingredient. The other part is an accompanying diluent vial containing ethanol, USP (35.4% w/w) and polysorbate 80, NF (b) (4). The contents of the two vials are intended to be reconstituted and further diluted in 5% dextrose or 0.9% sodium chloride before administration by intravenous infusion. Following table represents the DP components and composition.

**Presentations and Composition of Docetaxel for Injection**

Component	Weight/Vial	Fill Volume*	% Composition	Function
<b>Docetaxel, 80 mg/vial</b>				
<b>Active Vial</b> (b) (4) Docetaxel	80 mg	--	100%	API
<b>Diluent Vial</b> (b) (4) Ethanol, USP Polysorbate 80, NF	(b) (4)	4.0 mL	35.4% w/w (b) (4)	(b) (4)
<b>Docetaxel, 20 mg/vial</b>				
<b>Active Vial</b> (b) (4) Docetaxel	20 mg	--	100%	API
<b>Diluent Vial</b> (b) (4) Ethanol, USP Polysorbate 80, NF	(b) (4)	1.0 mL	35.4% w/w (b) (4)	(b) (4)

API = Active Pharmaceutical Ingredient  
 \*Overages are discussed in see Section 3.2.P.2.2.2.

A comparative composition between the RLD and the DP of this submission is provided. Sun Pharma developed a docetaxel for injection product that contains the same active and inactive ingredients (b) (4) as the RLD but differs in dosage form.

Applicant utilizes the experiences with RLD to develop Docetaxel injection for this submission. (b) (4)

The proposed DP manufacturing site is listed below:

Sun Pharmaceutical Industries Limited  
 Halol-Baroda Highway, Halol – 389350  
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Following are the container/closure system and the suppliers to be used for the finished DP.

Component	Supplier	DMF # and LOA
(b) (4)		

Not applicable

Two different acceptance criteria for DP impurities assay are proposed for release and for stability specification as in the following table.

Degradation Products	DP Release Limits	DP Stability Limits
Related substances <sup>4</sup> (HPLC)		(b) (4)
Assay of docetaxel (HPLC)		

Side-by-side comparison of several DP batches from Docefrez™ and RLD (Taxotere® ) have been provided up to 18 months in stability studies. The results suggest that all the known and unknown impurities of Docefrez™ (age of 24 months/ 18 months / 12 months at 2-8°C) are comparable to Taxotere® (available age) and also within the ICH limits (b) (4) where variable levels are observed in Docefrez™ compared to Taxotere®.

Three registration batches of each strength of docetaxel for injection and the accompanying diluents have been placed on stability according to the conditions, long-term (5 ± 3°C) and accelerated (25 ± 2°C/60 ± 5% RH), summarized in following Tables.

#### Stability Protocol Summary for Active Product Batches

Storage Conditions	Sampling Time (months)									
	0	1	2	3	6	9	12	18	24	36
25 ± 2°C/60 ± 5% RH	X	Y	Y	Z	X	-	-	-	-	-
15 ± 3°C	X	-	-	Y	Z	Y	X	-	-	-
5 ± 3°C	X	-	-	Y	Y	Y	X	Y	X	X

X = Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay, particulate matter, sterility, bacterial endotoxins.

Y= Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay

Z= Attributes to be tested: physical appearance, identification assay, (b) (4) reconstitution time, constituted solution, transmittance at (b) (4) absorbance at (b) (4) related substances, quantitative assay, particulate matter

#### Stability Protocol Summary for Diluent Batches

Storage Conditions	Sampling Time (months)									
	0	1	2	3	6	9	12	18	24	36
25 ± 2°C/60 ± 5% RH	X	Y	Y	Z	X	-	-	-	-	-
15 ± 3°C	X	-	-	Y	Z	Y	X	-	-	-
5 ± 3°C	X	-	-	Y	Y	Y	X	Y	Y	X

X = Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol, particulate matter, sterility, bacterial endotoxins.

Y= Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol.

Z = Attributes to be tested: physical appearance, identification assay, transmittance at (b) (4) absorbance at (b) (4) content of ethanol, particulate matter.

At present, 18-month long-term stability results are available for one batch of each strength and a 12-month long-term stability results are available for two batches of each strength. Six months of accelerated stability results are also available for each registration batch. Sun Pharma's stability protocol for the on-going ICH stability studies extends through the 36-month long-term time point and the 6-month accelerated time point.

No statistical analysis is included to support the proposed DP expiration dating. Applicant indicated to update the stability data as available. The Applicant proposes a (b)(4) expiration dating period for the Docetaxel for injection, when stored at long-term condition ( $5 \pm 3^{\circ}\text{C}$ ).

*Drug Product Critical Issues*

- New degradants in DP finished dosage form (lyophilized powder) and infusion solution, when compared with RLD batches.
- Check EES of DP sites for accuracy.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Two different acceptance criteria for DP impurities are proposed for release and for stability specification. Specifications need to be harmonized.
- Justification of (b)(4) expiration based on available stability data and whether ICH Q1E can be applied for this extrapolation.
- The DP labeling, which is submitted in PRL format, need to be evaluated for its relevant CMC sections.

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/investigational formulations section?	√		
14	Is there a Methods Validation package?	√		

15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMEPA/ODS <b>EER</b>

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

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

**Comments and Recommendations**

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker  
Pharmaceutical Assessment Lead (PAL)

June 17, 2009  
Date

Sarah Pope, Ph.D.  
Branch Chief

June 17, 2009  
Date

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/s/

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Haripada Sarker  
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