

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201525Orig1s000

CHEMISTRY REVIEW(S)

NDA 201525

Docetaxel Injection

Sandoz Inc.

Sue-Ching Lin

Review Chemist

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

**Chemistry, Manufacturing, and Controls (CMC)
Review of Original NDA
For the Division of Drug Oncology Products (HFD-150)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 201525
2. REVIEW #: 1
3. REVIEW DATE: 12-May-2011
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 102081 submission	N/A*
Pre-NDA meeting	02-Jul-2008

*The sponsor did not submit an original IND. The first submission for this IND was the meeting request for the 7/2/08 pre-NDA meeting

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	16-Sep-2010	17-Sep-2010
General correspondence (Update information regarding manufacturing sites, in response to FDA request.)	2	06-Oct-2010	06-Oct-2010
Amendment (SPL Labeling)	3	15-Nov-2010	15-Nov-2010
Amendment (Response to 03/15/11 CMC IR)	8	25-Apr-2011	25-Apr-2011
Amendment (Revised Container/carton labeling in response to DMEPA 4/21/11 comments and CMC 4/26/11 labeling comments)	9	29-Apr-2011	29-Apr-2011
Amendment (Response to 04/26/11 CMC IR)	10	06-May-2011	06-May-2011

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Inc.
Address: 506 Carnegie Center
Suite 400
Princeton, NJ 08540
Representative: Bernadette Attinger, Director of Regulatory Affairs
Telephone: (609) 627-8865
E-mail: Bernadette.attinger@parentarx.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: docetaxel injection
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5 (new formulation)
 - Submission Priority: S

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

Reference Listed Drug: NDA 20-449, Taxotere[®] (docetaxel) Injection
Concentrate, marketed by Sanofi-Aventis.

Taxotere[®] was originally approved in 1996 with 2-vial packages (single dose vial 80 mg/2 mL and diluent, and single dose vial 20 mg/0.5 mL and diluent). On 02-Aug-2010, one-vial formulation (without diluent) of Taxotere[®] was approved (single use vials 80 mg/4 mL and 20 mg/mL).

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: injection, solution

12. STRENGTH/POTENCY: 10 mg/mL (20 mg/2 mL, 80 mg/8 mL,
160 mg/16 mL)

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC

CMC Review Data Sheet

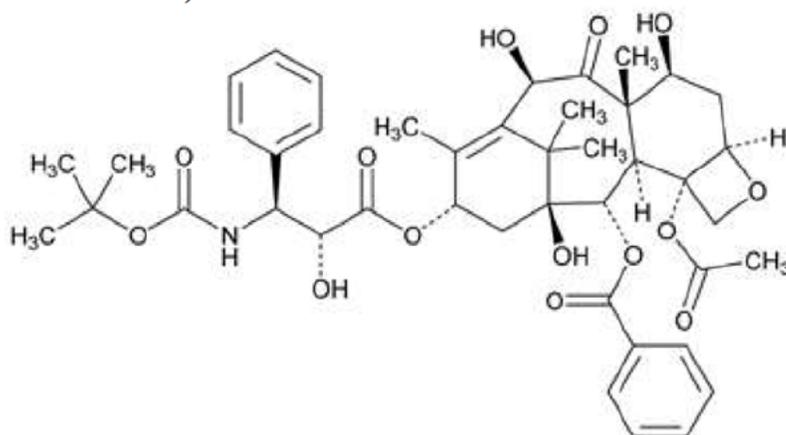
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

Not a SPOTS product

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

(The following structure was provided in the 4/25/11 amendment, in response to the FDA 3/15/11 comments.)



INN: Docetaxel

Chemical name: N-Debenzoyl-N-(*tert*-butoxycarbonyl)-10-deacetyltaxol

Other Chemical Names :

- Benzenepropanoic acid, β-[[1,1-dimethylethoxy)carbonyl]amino]-α-hydroxy-(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca-[3,4]benz[1,2-b]oxet-9-yl, ester, (α.R, β.S) (DMF Name)
- (2b,5b,7b,10b,13a)-4-Acetoxy-13-(((2R,3S)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl)oxy)-1,7,10-trihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate (Ph. Eur. Name)
- (2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2 benzoate

CAS Number: 114977-28-5

Molecular Formula: C₄₃H₅₃NO₁₄

Molecular Weight: 807.88 g/mol

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel drug substance	1	Adequate	12-May-2011	Reviewed by Sue-Ching Lin
	II	(b) (4)	(b) (4)	1	Adequate	09-May-2011	Reviewed by Sue-Ching Lin
	III	(b) (4)	(b) (4)	4	N/A	See current review	See section 3.2.P.7
	III	(b) (4)	(b) (4)	4	N/A	See current review	See section 3.2.P.7
	III	(b) (4)	(b) (4)	3	Adequate	21-Jan-2011	Reviewed by Amit Mitra
				3	Adequate	12-Apr-2007	Reviewed by Mark Sassaman
				3	Adequate	23-Mar-2007	Reviewed by Mark Sassaman
				3	Adequate	07-Jul-2009	Reviewed by Yichun Sun
				3	Adequate	03-Sep-2009	Reviewed by Ravindra Kasliwal
	V	(b) (4)	(b) (4)	3	Adequate	12-Aug-2010	Also included in the 4/8/11 microbiology review of this NDA.

¹ 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")

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

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102081	Submitted for pre-NDA meeting
NDA	20-449	Taxotere [®] (docetaxel) Injection Concentrate (Reference Listed Drug)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	26-Apr-2011	M. Stock
Pharm/Tox	All impurities are qualified at the proposed acceptance criteria*.	See note below	Sachia Khasar
Biopharm	Biowaiver is granted	26-Apr-2011	Angelica Dorantes
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Labeling comments to applicant	06-Apr-2011	Loretta Holmes
EA	Categorical exclusion is acceptable (see review)	11-May-2011	Raanan Bloom
Microbiology	Approval	08-Apr-2011	Bryan S. Riley

*See Dr. Sachia Khasar's e-mail response on page 100 of this review regarding related substances. This reviewer has discussed with Dr. Khasar the issue regarding the acceptance criterion for (b) (4) in the drug substance specification and Dr. Khasar has sent a pharm/tox information request to the applicant on May 9, 2011.

Executive Summary Section

The CMC Review for NDA 201525

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls (CMC), this NDA may be approved. Note that there is a pending Pharmacology/Toxicology (Pharm/Tox) issue regarding qualification of the proposed acceptance criterion for [REDACTED]^{(b) (4)} in the drug substance specification. From a CMC standpoint, the impact of the issue will be present only in the potential revision/updating of the [REDACTED]^{(b) (4)} specification and is not relevant to approvability of the NDA. The resolution of the issue will be captured in the Pharm/Tox review.

Based on the provided stability data, an 18-month expiration dating period is granted for the drug product when stored under the proposed storage condition (between 2°C and 25°C).

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

The drug substance used in this NDA is the anhydrous form of docetaxel, whereas the drug substance used in the manufacture of Taxotere[®] (the reference listed drug (RLD), NDA 20-449) is docetaxel trihydrate. The drug substance is prepared by semi-synthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Detailed information on the drug substance is referenced to DMF [REDACTED]^{(b) (4)}, held by [REDACTED]^{(b) (4)}. A letter of authorization (dated 04-Mar-2010) has been provided. DMF [REDACTED]^{(b) (4)} was reviewed by this reviewer on 12-May-2011 and found to be adequate to support this NDA .

A monograph for docetaxel trihydrate drug substance was added to the USP in February 2011. (At the time of this NDA submission, there was no monograph in the USP for docetaxel.) The proposed drug substance specification in this NDA has

Executive Summary Section

included all the tests (except (b) (4) in the current USP monograph with additional tests for (b) (4) is named “4-Epidocetaxel” (different numbering system) in the current USP monograph. The proposed acceptance criteria for assay and related substances are more stringent than the current USP limits.

All the (b) (4), with the exception of (b) (4) (which is not classified in ICH Q3C), meet ICH Q3C requirements. This reviewer has consulted the pharm/tox team (Dr. Sachia Khasar, pharm/tox reviewer, and Dr. Whitney Helms, pharm/tox team leader) regarding the acceptability of the proposed limit for (b) (4). This issue will be handled by the pharm/tox reviewer. Dr. Khasar has sent a pharm/tox information request to the applicant on May 9, 2011.

(2) Drug Product

The drug product, Docetaxel Injection, 10 mg/ml, is a sterile, non aqueous solution. The drug product will be available in multiple-use vials in three presentations: 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.

The drug product was developed as a “ready-to-use” alternative to Taxotere[®] Injection Concentrate (NDA 20-449) marketed by Sanofi Aventis. The NDA provides a comparison of Sandoz Inc’s formulation to the reconstituted solution (10 mg/mL) of Sanofi Aventis’s two-vial formulation (which consists of a docetaxel concentrate in one vial and a diluent in the other vial). Sandoz Inc’s Docetaxel Injection 10 mg/ml shows a lower concentration of polysorbate 80 and a higher concentration of ethanol 96% when compared to the RLD. Additionally polyethylene glycol 300 and anhydrous citric acid, which are not part of the RLD formulation, but are widely used for parenteral products, are components of Sandoz’s drug product.

It should be noted that while the concentration of the reconstituted solution of the two-vial formulation of Taxotere[®] (the RLD) is 10 mg/mL, the one-vial formulation of Taxotere[®] was approved on 02-Aug-2010 with a concentration of 20 mg/mL. In view of different concentrations of docetaxel injections available on the market, which can potentially cause confusions for health professionals, the FDA has recommended a special warning box to be present on the container labels and carton labeling for this product and other docetaxel injections.

The drug product is manufactured by compounding of the bulk solution, (b) (4) and filling, and packaging. The common bulk solution is (b) (4) the three product presentations (20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL).

The submitted stability data from 3 batches of each fill size support the proposed 18-month expiration dating period for the drug product when stored under the proposed condition (between 2°C and 25°C).

Executive Summary Section

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

The drug product is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer. Refer to the package insert for the proper use, as a single agent or in combination with other drugs.

This drug product requires no prior dilution with a diluent and is ready to add to 0.9% sodium chloride solution or 5% dextrose solution, prior to intravenous infusion. It is administered intravenously over one hour every 3 weeks.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information of the drug substance was referenced to DMF (b)(4), which has been reviewed by this reviewer and found to be adequate. The proposed drug substance specification is adequate pending an acceptable recommendation from the pharm/tox reviewer regarding the acceptance criterion for (b)(4).

All the inactive ingredients are USP/NF materials. Adequate data have been provided to ensure the quality of the drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The applicant does not propose a proprietary name for this drug product. This is acceptable as a proprietary name is not required for approval. The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. This reviewer had shared the labeling comments regarding container labels and carton labeling with the DMEPA reviewers before the labeling comments were conveyed to the applicant. The revised container labels and carton labeling, as amended by the applicant on 29-Apr-2011, are acceptable from the CMC perspective.

The Office of Compliance has issued an overall “acceptable” recommendation for all facilities used for manufacturing and control of the drug substance and drug product.

Executive Summary Section

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

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

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

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

C. CC Block: entered electronically in DARRTS

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/s/

SUE CHING LIN
05/12/2011

SARAH P MIKSINSKI
05/16/2011

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

OND Division: Division of Drug Oncology Products
NDA: 201-525
Applicant: Sandoz Inc.
Letter Date: 16 September, 2010
Stamp Date: 17 September, 2010
PDUFA Goal Date: 17 July, 2010 (standard)
Mid-Cycle Review Data: 17 February, 2010 (standard)
Tradename: Not proposed
Established Name: Docetaxel Injection
Dosage Form/Strength: Solution; 10mg/mL (20mg/2mL, 80mg/8mL, 160mg/16mL)
Route of Administration: IV
Indication: Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC. Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC. Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer. Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction. Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

Regulatory Filing For 505 (b) (2)
Related IND IND 102,081

Assessed by: Haripada Sarker
Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

The application, Sandoz (formerly Ebewe Parenta Pharmaceutical) introduces the drug product, Docetaxel Injection, which is supplied as 10mg/ml solution concentrate of three strengths (20mg/2mL, 80mg/mL and 160mg/16mL) in vials. The final drug product is a clear and sterile solution intended for infusion after dilution. Docetaxel (Taxotere) injection by Sanofi Aventis is the reference listed drug (RLD), which 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.

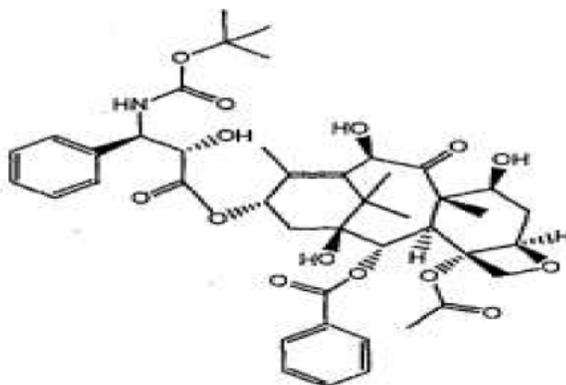
Taxotere® under NDA 20-449 (RLD) is equivalent in dosage form, and formulated as injection (40mg base/mL). Sandoz's Docetaxel Injection 10 mg/mL differs from the originator (RLD) in the amounts of polysorbate 80 and ethanol 96%. Sandoz Inc.'s Docetaxel Injection 10 mg/mL contains less polysorbate 80 and more ethanol 96% when compared to the RLD. Additionally, polyethylene glycol 300 is a solubilizer and anhydrous citric acid is used for pH adjustment. Both are widely used for parenteral products and are components of Ebewe's formulation. Ebewe Pharma, (Unterach, Austria) is the intended site for manufacturing of this drug product. On April, 27, 2008 Ebewe Pharma submitted to the Agency a Pre-NDA Meeting Packet for Docetaxel Injection ready to use formulation.

In pre-NDA meeting response dated June 26, 2008 under NDA 201-525, the only CMC issue was related to DP stability. Applicant proposed the DP stability plan, which was found to be acceptable. The CMC information of this NDA is submitted in eCTDQ format.

Drug Substance (DS)

The DS is a sterile bulk. Applicant referred to DMF (b) (4) (Type II) for DS CMC information. In the NDA submission, Applicant provided brief DS information regarding identity, physico-chemical properties and specifications. Docetaxel is an optically active compound. It is a semi-synthetic drug substance made from a natural precursor. 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. In solution, docetaxel is known to undergo pH (b) (4)

(b) (4) A couple of DS structurally related impurities are indicated in the submission. Request has been made to Office of Compliance to confirm cGMP status for the DS related sites listed in the submission. The DS is identified with following structure.



DS is manufactured by (b) (4). It is noted that two other DMFs are cross-referenced for intermediates of the DS. DMF (b) (4); Manufacture of (b) (4)

(b) (4) the finished DS. Data from three DS batches are included along with justification of specification.

DS Critical Issues

- In solution, docetaxel is known to undergo pH (b) (4), leading to the formation of variety of isomers. Degradation products of docetaxel should be evaluated as per ICH Q3A (R).
- EER information for DS needs to be re-examined for accuracy.
- DS manufacture from (b) (4) should be verified for comparability.
- The cross-referenced DMFs (b) (4) for intermediates in Type II DMF (b) (4) should be evaluated, and EES should be requested if necessary.
- In addition, determination of starting material for DS is not clear. Verification of DS starting material should be assessed.

Drug Product (DP)

Docetaxel Injection, 10 mg/ml, is a sterile, non aqueous solution intended for infusion after dilution. The drug product will be available in three presentations of 20 mg/vial, 80 mg/vial and 160 mg/vial, resulting in volumes of 2 mL (Docetaxel Injection 20 mg/2 mL), 8 mL (Docetaxel Injection 80 mg/8 mL) and 16 mL (Docetaxel Injection 160 mg/16 mL). A comparative composition between the RLD and the DP of this submission is provided (Table 1).

Since the submission of this Pre-NDA Meeting Packet Ebewe Pharma indicated the change in the formulation to allow for the addition of Citric Acid Anhydrous, USP. Due to the addition of Citric Acid Anhydrous, USP some of the other excipients have been slightly altered.

Table 1: Comparison of Ebewe Pharma's formulation to the RLD		
	Proposed Ebewe Drug Product (Docetaxel) 10mg/mL	Reference Listed Drug (Taxotere) 40 mg/mL Base (10mg/ml after dilution)
Active	Docetaxel	Docetaxel
Excipients	Polysorbate 80	Polysorbate 80
	Polyethylene glycol 300	N/A
	Ethanol 96% (v/v)	N/A
	Citric Acid, anhydrous	N/A
Diluent	N/A	13% Ethanol in water for injection solution

The compositions of the Docetaxel Injection 10 mg/mL presentations are provided. This initial diluted solution (10 mg/mL) needs to be further diluted with an appropriate volume of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to produce a final dilution for IV infusion. Applicant utilizes the DP pharmaceutical development experiences of RLD to develop Docetaxel injection for this submission. The manufacturing and controls for RLD and the DP appears to be very similar.

The proposed DP manufacturing site is listed below:

Ebewe Pharma Ges.m.b.H. Nfg.KG
Mondseestrasse 11
A-4866 Unterach, Austria

Docetaxel Injection 10 mg/mL will be packaged in Type I, clear, colorless, glass vials with grey, (b) (4) rubber stoppers. The vials will be sealed with an aluminum crimp cap with a flip-off cap. An overview of the proposed container closure systems and the corresponding DMF references are provided. Single specification is proposed for release and for stability as following.

Table 2: DP Release and Shelf-Life Specification for Docetaxel Injection 10 mg/mL; 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL

Test	Method	Release and Shelf-Life Specifications		
Appearance	Visual	Clear, colorless to pale yellow solution		
Clarity of solution		(b) (4)		
Colour of solution				
Visible particles				
Sub-visible particles				
Extractable volume				
pH				
Density ¹				
Identity of Docetaxel				
Content of Ethanol				
Content of Docetaxel				
				(b) (4)

NMT: Not More Than; NLT: Not Less Than; HPLC: High-Performance Liquid Chromatography;
TLC: Thin-Layer-Chromatography; GC: Gas Chromatography.
EU: 1 Endotoxin Unit [EU]

(b) (4)

¹ Only tested at release, not part of shelf-life specification

² Method I and Method II

³ Controlled as unknown impurity to NMT (b) (4) at release, specified only during shelf-life

Stability Summary for both Docetaxel solutions is provided for long term and accelerated conditions as following. Stability test data are provided for 9 batches, 12 months for long term and 6 months for accelerated condition for the finished DP. No significant change in purity was observed. Stability data also provided for Docetaxel Injection 10 mg/mL. The data indicate that Docetaxel Injection 10 mg/mL appeared stable for up to 4 hours at 2 to 8°C and at room temperature (20 to 25°C) when prepared in infusion solutions of glucose 5% and sodium chloride 0.9% at concentrations of 0.3 mg/mL and 0.74 mg/mL.

No statistical analysis is included to support the proposed DP expiration dating. Applicant indicated

to update the stability data as available. The Applicant proposes an 18-month expiration dating period for the Docetaxel solution (10 mg/mL), when stored not above 25°C (77°F).

Drug Product Critical Issues

- New degradants in DP concentrate (finished dosage form) and infusion solution, when compared with RLD specification.
- Check EES of DP sites for accuracy.
- DMFs for DS manufacturing and container/closure systems need to be reviewed for adequacy of the NDA.
- Check stability test data on drug product infusion solution over the period of intended storage time.
- Check in-use stability data for the drug product infusion solution.
- Justification of 18-months expiration based on 6-months stability data in the submission and an update. Whether ICH Q1E can be applied for this extrapolation to justify the proposed expiration.
- The DP labeling, applicant proposes DP storage not above 25°C (36 to 77°F). Justify the statement.
- Harmonize release and stability specifications for impurities.

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?	√		Pending review of stability update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Review issue.
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 Biopharm

		√ √ √	Statistics (stability) OCP/CDRH/CBER LNC DMEPA EER
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Have all DMF References been identified? Yes (√) No ()

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

Comments and Recommendations

The application is fileable, no 74-Day Letter issues regarding drug product stability have been identified at this point. However, the issue of DS intermediate and the corresponding DMFs should be communicated to applicant as appropriate. 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, Ph.D.
CMC Lead

November 5, 2010
Date

Sarah Pope Miksinski, Ph.D.
Branch Chief

November 5, 2010
Date

APPEARS THIS WAY ON ORIGINAL

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

/s/

HARIPADA SARKER
11/05/2010

SARAH P MIKSINSKI
11/08/2010