

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201525Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 201-525	<b>Reviewer:</b> Angelica Dorantes, Ph.D	
<b>Submission Date:</b>	September 16, 2010	<b>Supervisor:</b> Patrick J. Marroum, Ph.D	
<b>Division:</b>	DDOP	<b>Date Assigned:</b>	October 20, 2010
<b>Sponsor:</b>	Sandoz, Inc.	<b>Date of Review:</b>	April 22, 2011
<b>Trade Name:</b>	Docetaxel Injection 10 mg/ml	<b>Type of Submission:</b> 505 (b)(2) NDA	
<b>Generic Name:</b>	Docetaxel		
<b>Indication:</b>	Docetaxel is used for the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.		
<b>Formulation/strengths</b>	Injectable Solution/vial 20 mg/2 ml, 80 mg/8 ml and, 160 mg/16 ml		
<b>Route of Administration</b>	Intravenous		
<b>Type of Review:</b>	<b>BIOWAIVER REQUEST</b>		

**SUBMISSION:**

Sandoz submitted NDA 201-525 for Docetaxel Injection 10 mg/ml in the following presentations: 20 mg/2ml, 80 mg/8 ml, and 160 mg/16 ml under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. This NDA 505 (b)(2) application relies for its approval on the FDA's findings of safety and effectiveness for the Reference Listed Drug, Taxotere® for Injection, NDA 20-449 of Sanofi-Aventis U.S L.L.C. This product has the same dosage form (i.e., injectable solution) as the Reference Listed Drug. This product is intended for the same indications, dosage regimen and route of administration as Taxotere®. The proposed indication for Docetaxel injection is the treatment of various types of cancers like breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

**BIOPHARMACEUTICS:**

**Formulation:** Docetaxel Injection, 10 mg/ml, is a sterile, non aqueous ready to use solution intended for infusion after dilution. Docetaxel Injection 10 mg/ml is available as 20 mg/2 ml, 80 mg/8 ml and 160 mg/16 ml. Each 1 ml contains 10 mg docetaxel; 80 mg polysorbate 80; 648 mg polyethylene glycol 300; 275.9 mg ethanol 96% (v/v) and 4 mg anhydrous citric acid.

The next table presents the formulations for the 20 mg/2 ml, 80 mg/8 ml and 160 mg/16 ml products.

Ingredients	Docetaxel Inj 20mg/2 ml	Docetaxel Inj 80mg/8 ml	Docetaxel Inj 160mg/16 ml
Docetaxel (anhydrous)	20 mg	80 mg	160 mg
Citric acid (anhydrous)	(b) (4)		
<b>Polyethylene Glycol 300</b>			
Polysorbate 80			
Ethanol 96%			
Final Volume	2 ml	8 ml	16 ml

The comparison of the formulations for the RLD product, Taxotere® and proposed Docetaxel Injection product are described in the table below.

	Proposed Sandoz Drug Product (Docetaxel Injection 10mg/ml)		Originator Product (Taxotere®) Premix Solution 10 mg/mL		Function
<b>Active</b>	Docetaxel	10.0 mg	Docetaxel	10.0 mg	Active
<b>Excipients</b>	Polysorbate 80	80.0 mg	Polysorbate 80	260.0 mg	(b) (4)
	Polyethylene Glycol 300	648.0 mg	N/A	-	
	Anhydrous Citric Acid	4.0 mg	N/A	-	
	Ethanol 96% v/v <sup>1</sup>	275.9 mg (absolute: 258.9 mg)	N/A	-	
<b>Diluent</b>	N/A		13% (w/w) solution of Ethanol 95% (v/v) in water <sup>2</sup>	735.6 mg (absolute 88.3 mg)	
<b>Total:</b>		1,017.9 mg		1,005.6 mg	

Sandoz's Docetaxel Injection product differs in excipients other than those allowed in 21 CFR 314.94(a)(9)(iii); (preservative, buffer or anti-oxidant). In addition Sandoz Inc is proposing an additional packaging size, 160 mg/16 ml that is not part of the Taxotere NDA 20-449.

Sandoz Inc's Docetaxel Injection 10 mg/ml differs from the originator in the amounts of polysorbate 80 and ethanol 96%: Sandoz Inc's Docetaxel Injection 10mg/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 widely used for parenteral products are also part of the formulation.

**BIOWAIVER:**

In this NDA submission, Sandoz is requesting a waiver from the CFR's requirement of providing in vivo bioequivalence data for their Docetaxel Injection product relative to the reference listed drug (RLD), Taxotere®. Docetaxel Injection is a parenteral solution intended solely for administration by injection. The formulations of the RLD and the proposed drug product differ in excipients. The proposed drug product differs from the RLD in that the RLD is provided as a viscous concentrated solution packaged with a diluent, and the proposed Sandoz product is ready to use. Due to this difference the formulation is also slightly different with respect to the addition of the excipients Polyethylene glycol 300 and citric acid and a higher concentration of ethanol. All excipients as present in the formulation are still within the acceptable IIG (Inactive Ingredient Guide) limits.

Additionally, please note that on June 26, 2008, FDA agreed that no further nonclinical or clinical studies were required to support the approval of this product (*FDA responses to sponsor's Pre-NDA questions*).

**RECOMMENDATION:**

The Biopharmaceutics group at the Office of New Drug Quality Assessment (ONDQA) has reviewed the information included in NDA 201-525 for Docetaxel Injection 10 mg/ml. Based on the Agency's CFR 320.22(b)(1) regulations and the information showing that **1)** Sandoz's Docetaxel formulation has the same concentration of the active ingredient as the Taxotere® formulation and is provided as a single dose vial, sterile, pyrogen-free solution and all the inactive ingredients are within IIG limits, **2)** the route of administration, dosage form and indications of their product are the same as the RLD product, ONDQA-Biopharmaceutics considers that the in vivo BA/BE of the Sandoz's Docetaxel Injection product is self-evident. Therefore, the sponsor's request for a biowaiver for their Docetaxel Injection 10 mg/ml (20 mg/2 ml, 80 mg/8 ml, and 160 mg/16 ml) product is acceptable and the biowaiver is granted.

**Angelica Dorantes, Ph. D.**  
Biopharmaceutics Team Leader  
Office of New Drugs Quality Assessment

**Patrick J. Marroum, Ph. D.**  
Biopharmaceutics Supervisor  
Office of New Drugs Quality Assessment

cc: NDA 201-525

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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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ANGELICA DORANTES  
04/26/2011

PATRICK J MARROUM  
04/26/2011

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## Clinical Pharmacology Review

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<b>NDA</b>	201525/SDN1/000
<b>Submission Date:</b>	9/16/10
<b>Brand Name:</b>	Docetaxel Injection™
<b>Generic Name:</b>	Docetaxel
<b>Formulation:</b>	One vial docetaxel injection 10 mg/mL (20 mg/2mL, 80 mg/8 mL and 160 mg/16 mL)
<b>OCP Reviewer:</b>	Jeanne Fourie Zirkelbach, PhD
<b>OCP Team Leader:</b>	Qi Liu, PhD
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Drug Oncology Products
<b>Sponsor:</b>	Sandoz Inc.
<b>Submission Type; Code:</b>	Original Submission
<b>Dosing regimen:</b>	IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m <sup>2</sup> , Non-small cell lung cancer: 75 mg/m <sup>2</sup> , Hormone Refractory Prostate cancer: 75 mg/m <sup>2</sup> , Gastric adenocarcinoma: 75 mg/m <sup>2</sup> Squamous cell carcinoma of the head and neck: 75 mg/m <sup>2</sup>
<b>Indication:</b>	Breast cancer, non-small cell lung cancer and hormone refractory prostate cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck.

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## 1 EXECUTIVE SUMMARY

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Sandoz Inc. submitted an original New Drug Application (NDA 201525/S-000/SDN1) for Docetaxel Injection® 10 mg/mL.

Based on the comparison to the listed drug (Taxotere® for Injection; two vial formulation; Sanofi-Aventis), Sandoz was granted a waiver of the bioequivalence requirements for Docetaxel Injection® in accordance with 21 CFR 320.22 (b)1. Since the Sandoz drug product is pharmaceutically equivalent to the listed drug, the current 505(b)(2) application did not include clinical studies and relies on the FDA's findings of safety and effectiveness for Taxotere® for Injection (two vial formulation consisting of one vial concentrate and one vial diluent; NDA 20-449).

**The Sandoz product is proposed for use in all of the indications listed for the reference drug product (Taxotere® for injection) as follows:**

- Breast Cancer: Indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Docetaxel in combination with Doxorubicin and Cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.
- Non-Small Cell Lung Cancer: As a single agent Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. In combination with Cisplatin, Docetaxel is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.
- Hormone Refractory Prostate Cancer: In combination with Prednisone, Docetaxel is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.
- Gastric Adenocarcinoma: In combination with Cisplatin and Fluorouracil for untreated, advanced gastric cancer, including the gastroesophageal junction.
- Squamous cell carcinoma of the head and neck cancer: With cisplatin and fluorouracil for induction treatment of locally advanced cancer.

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 reviewed the information contained in NDA 201525 (SDN 1). This submission is considered acceptable from a clinical pharmacology perspective.

#### Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

## 1.2 PHASE IV COMMITMENTS

None.

## 1.3 REGULATORY BACKGROUND

- The listed drug that is the basis for this NDA submission is Taxotere®, marketed by Sanofi-Aventis (NDA 020-449; approved May 1996).
- A preNDA meeting for the current application was held on 5/27/08, however there are no previous Clinical Pharmacology reviews for this NDA in DARRTS. As agreed in the FDA's response to the pre-NDA meeting briefing package questions, no clinical studies are required, as the differences in excipients compared to the listed drug do not affect the safety or efficacy of the proposed drug product.

## 1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The one vial formulation of Taxotere was approved on 8/2/10, which was subsequent to the date on which the current submission was submitted. Therefore, the applicant used the two vial formulation of Taxotere® (docetaxel) injection concentrate (NDA 20,449) as the listed product in the current submission.

The two vial Taxotere formulation consists of a docetaxel concentrate vial and a diluent vial. Taxotere is highly viscous and consists of 40 mg/mL docetaxel in polysorbate 80. The Taxotere® diluent is a 13% ethanol and water for injection mixture. Prior to administration of Sanofi-Aventis' Taxotere® two dilution steps are required. The concentrate must be diluted initially with the ethanol/water diluents resulting in a 10 mg/mL docetaxel solution. The solution is then further diluted with sodium chloride 0.9% or dextrose 5% before administration.

Sandoz Inc, has developed a ready to use Docetaxel Injection 10 mg/mL drug product. Table 1 below compares the Sandoz formulation with the reference drug (Taxotere® (docetaxel) Injection Concentrate) and Table 2 below lists the composition of the Sandoz formulation. The Sandoz product contains the same active ingredient as the listed drug. The proposed product differs in excipients other than those allowed in 21 CFR 314.94(a)(9)(iii); (preservative, buffer or anti-oxidant). Specifically, the proposed product is different from the listed drug with respect to the addition of the excipients polyethylene glycol 300 and citric acid and it has a higher concentration of ethanol. The proposed product has a PS80:Taxotere ratio of 8:1 vs. 26:1 for the listed drug. Based on the preNDA review, no clinical studies are required based on the differences in excipients compared to the listed drug.

The proposed drug product further differs from the listed drug in that the listed drug is provided as 20 mg/0.5 mL and 80 mg/2 mL concentrate (20 mg/2 mL and 80 mg/8 mL after addition of the diluent), while the proposed product is supplied as a 10 mg/mL ready to use product in 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL presentations.

The Reviewer's analysis suggests that the change in the unbound docetaxel fraction, caused by the decreased amount of PS80 in the Sandoz formulation vs. Taxotere, is not likely to have a

significant effect on the pharmacokinetics of docetaxel (See Section 2.5.2.1 below).

**Table 1. Comparison of the proposed and listed product formulations.**

	Proposed Sandoz Drug Product (Docetaxel Injection 10mg/ml)		Originator Product (Taxotere®) Premix Solution 10 mg/mL		Function
Active	Docetaxel	10.0 mg	Docetaxel	10.0 mg	Active
Excipients	Polysorbate 80	80.0 mg	Polysorbate 80	260.0 mg	(b) (4)
	Polyethylene Glycol 300	648.0 mg	N/A	-	
	Anhydrous Citric Acid	4.0 mg	N/A	-	
	Ethanol 96% v/v <sup>1</sup>	275.9 mg (absolute: 258.9 mg)	N/A	-	
Diluent	N/A		13% (w/w) solution of Ethanol 95% (v/v) in water <sup>2</sup>	735.6 mg (absolute 88.3 mg)	
Total:		1,017.9 mg		1,005.6 mg	

**Table 2. Proposed formulation of Sandoz docetaxel injection**

Proposed Docetaxel Injection Formulation				
Ingredient	Function	20 mg/2 mL	80 mg/8 mL	160 mg/16 mL
Docetaxel	Active	20.00 mg	80.000 mg	160.000 mg
Anhydrous Citric Acid				(b) (4)
Polysorbate 80				
Polyethylene Glycol 300				
Ethanol 96% (v/v)				
				(b) (4)

<sup>1</sup> Ethanol 96% v/v = Ethanol (b) (4) w/w

<sup>2</sup> 13% w/w solution of Ethanol 95%(v/v) = Ethanol (b) (4) w/w

**Signatures:**

Reviewer: Jeanne Fourie Zirkelbach, PhD  
Division of Clinical Pharmacology 5

Team Leader: Qi Liu, PhD  
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - J Mwidau; MTL - P Cortazar; MO - K Snyder,  
DCP- Reviewers - J Fourie Zirkelbach,  
5: DDD - B Booth  
DD - A Rahman

## **2 QUESTION BASED REVIEW**

Note: Only relevant sections were completed.

### **2.1 GENERAL ATTRIBUTES**

- 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**
- 2.1.2 What are the proposed mechanisms of action and therapeutic indications?**
- 2.1.3 What are the proposed dosage(s) and route(s) of administration?**

### **2.2 GENERAL CLINICAL PHARMACOLOGY**

- 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**
- 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?**
- 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**
- 2.2.4 Exposure-response**

### **2.3 INTRINSIC FACTORS**

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**
- 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

- 2.3.2.1 Pediatric patients**
- 2.3.2.2 Renal impairment**
- 2.3.2.3 Hepatic impairment**
- 2.3.2.4 What pregnancy and lactation use information is there in the application?**

## **2.4 EXTRINSIC FACTORS**

- 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**
- 2.4.2 Drug-drug interactions**

## **2.5 GENERAL BIOPHARMACEUTICS**

- 2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.5.2 What is the composition of the to-be-marketed formulation?**

See the Clinical Pharmacology Summary, for the quantitative and qualitative comparisons between docetaxel injection and the listed drug.

- 2.5.2.1 Can the change in the unbound fraction of docetaxel, caused by the decreased concentration of PS80 in the Sandoz formulation vs. Taxotere, have a significant effect on the pharmacokinetics of docetaxel?**

No. The following Reviewer's analysis is aimed to answer this question and is similar to the analysis performed in the recent Taxotere Citizen Petition 2010.

As detailed in Table 1 and Table 2 above, Sandoz Inc's Docetaxel Injection 10 mg/mL differs from the listed drug in the amounts of polysorbate 80 and ethanol 96%: Sandoz Inc's Docetaxel Injection 10mg/mL shows a lower concentration of polysorbate 80 and a higher concentration of ethanol 96% when compared to the listed drug. Additionally, polyethylene glycol 300 and anhydrous citric acid are components of Sandoz's formulation.

The ratio of PS80:docetaxel in 505(b)(2)s to date have been within ranges of 26:1 to 27:1 (that of the listed drug: 2-vial and 1-vial formulations), but the ratio of PS80:docetaxel of Sandoz's product is 8:1.

Docetaxel binds to human serum albumin, AAG and lipoproteins, and therefore, PS80 can increase free docetaxel concentration by binding to AAG and replacing docetaxel from AAG. The reviewer examined whether the ratio of PS80:docetaxel in Sandoz's formulation would affect pharmacokinetic profile of docetaxel.

*In vitro* binding results from Loos et al. (1) show that at a PS80 concentration of 1.0  $\mu\text{L}/\text{mL}$  the unbound fraction will increase from 6.95 to 7.84% compared to the formulation where no PS80 is present (“none” in Table 3).

**Table 3. Extent of binding of docetaxel to human plasma proteins as a function of polysorbate 80 (1).**

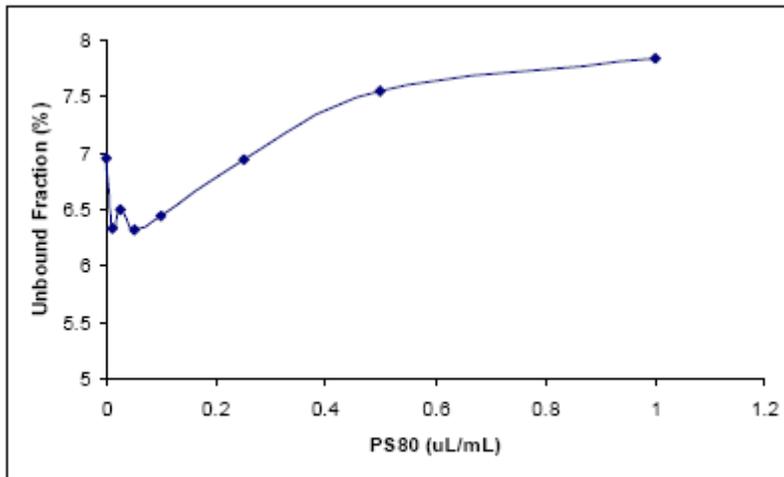
<i>Polysorbate 80</i> ( $\mu\text{L}/\text{mL}$ )	<i>Fraction unbound</i> (%, mean $\pm$ SD)	<i>Percentage of reference</i> value*	<i>Significance</i>
None	6.95 $\pm$ 0.0678	100	
0.010	6.34 $\pm$ 0.0241	91	†
0.025	6.50 $\pm$ 0.182	93	†
0.050	6.32 $\pm$ 0.281	91	†
0.10	6.44 $\pm$ 0.198	93	†
0.25	6.94 $\pm$ 0.154	100	
0.50	7.55 $\pm$ 0.189	109	‡
1.0	7.84 $\pm$ 0.0752	113	‡

Data are presented as mean  $\pm$  SD of triplicate observations (except for none, 0.010  $\mu\text{L}/\text{mL}$ , and 0.50  $\mu\text{L}/\text{mL}$  [duplicate each]).

\*None is considered as the reference value (i.e. no polysorbate 80 added).

†Significantly lower than none (1-way ANOVA, followed by Duncan’s multiple range test).

‡Significantly higher than none (1-way ANOVA, followed by Duncan’s multiple range test).



**Figure 1. Table 3 values presented graphically.**

**Table 4. PS80 concentration in plasma when the plasma volume is 3000 mL**

	Ratio PS80:Docetaxel		
	8:1	26:1	27:1
PS80 concentration in plasma ( $\mu\text{L}/\text{mL}$ )	0.032	1.04	1.08

A: Example calculation:

An adult with a BSA of 1.7 m<sup>2</sup> (average BSA)

- Will receive 127.5 mg docetaxel (75 mg/m<sup>2</sup> x 1.7 m<sup>2</sup>)
- And 1020 mg of PS80 (127.5 mg x 8, when the PS80:docetaxel ratio is 8:1).

If this person has a 3000 mL plasma volume the concentration (w/v) of PS80 in plasma will be 0.34 mg/mL (1020 mg / 3000 mL).

Since the density of PS80 is 1.06 g/mL (1.06 mg/ $\mu\text{L}$ ), the PS80 concentration (v/v) is 0.32  $\mu\text{L}/\text{mL}$  (0.34 mg/mL/1.06 mg/ $\mu\text{L}$ ).

The percent fraction unbound reaches a plateau at > 0.5  $\mu\text{L}/\text{mL}$  PS80 and the 0.32  $\mu\text{L}/\text{mL}$  PS80 concentration appears to be on the up-slope of the function (see Figure 3). However, the unbound fraction of docetaxel varies widely among patients with a median (range) of 4.0% (1.2 to 22.6%) (2). Therefore, the minor change in the unbound docetaxel fraction, caused by the formulation difference in PS80, is not likely to have a significant effect on the pharmacokinetics of docetaxel.

References:

1. Loos WJ, *et al.* (2003) Clin. Pharmacol. & Ther 74(4):364-371
2. Minami, H, *et al.* (2006) Cancer Sci 97(3):235-241

### 2.5.3 What moieties should be assessed in bioequivalence studies?

The applicant was informed by FDA during the preNDA meeting (5/27/08) that a bioequivalence study with the listed drug is not required as the difference in excipients, compared to the listed drug, do not affect the safety or efficacy of the proposed drug product. This submission did not include clinical studies and relies on the FDA's findings of safety and effectiveness for the two vial formulation of Taxotere® for Injection (NDA 20-449).

### 2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

### 2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

## 2.6 ANALYTICAL SECTION

- 2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
- 2.6.2 Which metabolites have been selected for analysis and why?
- 2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
- 2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/cder/guidance/4252fnl.pdf> )
  - 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
  - 2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
  - 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
  - 2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
  - 2.6.4.5 What is the QC sample plan?

## 3 DETAILED LABELING RECOMMENDATIONS

FDA based labeling for the Sandoz drug product on the recently approved one vial formulation of Taxotere (80 mg/4 mL and 20 mg/mL), which was approved on 8/2/10.

Only relevant Clinical Pharmacology sections are shown in track change format below. The sponsor's proposed changes from the most recent Taxotere label are underlined. FDA recommended changes are **underlined and bolded**.

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

## 4 APPENDICES

### 4.1 NDA FILING AND REVIEW FORM

<b>General Information About the Submission</b>				
<b>NDA Number</b>	201525	<b>Brand Name</b>	Docetaxel Injection®	
<b>DCP Division (I, II, III, IV, V)</b>	V	<b>Generic Name</b>	Docetaxel	
<b>Medical Division</b>	Oncology	<b>Drug Class</b>	Microtubule Stabilizer	
<b>OCP Reviewer</b>	Jeanne Fourie Zirkelbach, PhD	<b>Indication(s)</b>	Breast cancer, non-small cell lung cancer and hormone refractory prostate cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck.	
<b>OCP Team Leader</b>	Qi Liu, PhD	<b>Dosage Form</b>	One vial docetaxel injection 10 mg/mL (20 mg/2mL, 80 mg/8 mL and 160 mg/16 mL)	
<b>Date of Submission</b>	9/16/2010	<b>Dosing Regimen</b>	IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m <sup>2</sup> , Non-small cell lung cancer: 75 mg/m <sup>2</sup> , Prostate cancer: 75 mg/m <sup>2</sup> , Gastric adenocarcinoma: 75 mg/m <sup>2</sup> , Head and Neck Cancer: 75 mg/m <sup>2</sup> .	
<b>Due Date of OCP Review</b>		<b>Route of Administration</b>	Intravenous infusion	
<b>Standard PDUFA Due Date</b>		<b>Sponsor</b>	Sandoz Inc.	
<b>Clinical Pharmacology Information</b>				
	<b>"X" if included at filing</b>	<b>Number of studies submitted</b>	<b>Number of studies reviewed</b>	<b>Critical Comments If any</b>
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>QTC studies:</b>				
<b>In-Vitro Release BE</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Biliary Elimination</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				
Filability and QBR comments				
	"X" if yes	<b>Comments</b>		
<b>Application filable?</b>	X			
<b>Comments sent to firm?</b>				
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>	J Fourie Zirkelbach, Ph.D.			
<b>Secondary reviewer Signature and Date</b>	Q Liu, Ph.D.			

CC: HFD-150 (CSO –J Mwidau; MTL– P Cortazar; MO –K Snyder)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD - B Booth; DD - A Rahman)

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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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JEANNE FOURIE  
04/08/2011

QI LIU  
04/08/2011