CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205934Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: November 20, 2015
From: Wimolnut Manheng, PhD, DABT
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
(Division of Oncology Products 1)
Office of Hematology and Oncology Products (OHOP)
Re: Addendum to Primary Pharmacology/Toxicology Review
NDA: 205934
Drug: Docetaxel injection, non-alcohol formula
Indications: Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, head and neck cancer
Applicant: Teikoku Pharma USA, Inc.

This addendum to the original pharmacology/toxicology review of the NDA is to clarify the available strengths approved for Taxotere (see Section 1.1 of the NDA review) and correct the cross-references to table error in the original review (see Section 2.3 of the NDA review). The original review language and corrected language are provided below. The strikeout text was removed from the original version and was replaced with the text in bold.

Section 1.1 Introduction in the original review dated 10/22/2015 reads:

"Docetaxel is a microtubule inhibitor that was approved by the US FDA 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. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cell.

The Applicant, Teikoku Pharma USA, Inc. (TPU), has submitted this 505(b)(2) NDA for a docetaxel injection, non-alcohol formula (also referred to as TPU-004DO) that is intend to be used via the same intravenous (IV) route, at the same dose levels and for the same indications as the listed drug (LD), Taxotere. TPU's to-be-marketed formulation that is the subject of this NDA is different from the Taxotere drug product formulation, in that it will be supplied as an alcohol-free alternative to Taxotere, containing the same active ingredients as the LD, but containing soy bean oil rather than dehydrated alcohol solution. Docetaxel injection also contains polyethylene glycol and (b)(4) citric acid. Docetaxel injection will be supplied in 3 strengths which are 20 mg/mL, 80 mg/4 mL, and 160 mg/8 mL. ~~However, there are only 2 strengths approved for Taxotere, which are 20 mg/mL and 80 mg/4mL.~~ The preparation and administration of docetaxel injection are also the same as the LD. The injection

(b)(4) is injected into a 250 mL infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

TPU has included in this NDA a request for a waiver of in vivo bioequivalence (BE) (eCTD 1.12.15) for docetaxel injection. The biowaiver request was discussed in a pre-NDA meeting (August 19, 2013), in which the Agency indicated that such a waiver may be granted if TPU submitted a side-by-side comparison of CMC and biopharmaceutical characteristics of the LD and TPU's product in the final infusion solution to be administered to patients. TPU submitted a report from a GLP-compliant single-dose pharmacokinetic (PK) study comparing docetaxel injection and Taxotere in male Beagle dogs. TPU also submitted reports from a non-GLP PK study in dogs, a human plasma protein binding study and a GLP in vitro complement activation study in human serum, comparing their product to Taxotere."

The corrected section 1.1 Introduction which replaces the previous version reads:

"Docetaxel is a microtubule inhibitor that was approved by the US FDA 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. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cell.

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single-dose pharmacokinetic (PK) study comparing docetaxel injection and Taxotere in male Beagle dogs. TPU also submitted reports from a non-GLP PK study in dogs, a human plasma protein binding study and a GLP in vitro complement activation study in human serum, comparing their product to Taxotere."

Section 2.3 Drug Formulation in the original review dated 10/22/2015 reads:

Docetaxel injection contains the same active ingredient as the LD but differs in the inactive ingredients (Table 1, Table 2, Table 3). The compositions of 3 strengths for docetaxel injection are presented in ~~**Error! Reference source not found.**~~, including the excipients. The amount of polysorbate 80 in docetaxel injection is slightly higher than in the LD (b)(4)). The final concentration of polysorbate 80 in the diluted product (ready to infuse) is within the permissible limits of FDA's inactive ingredients guide (IIG) for intravenous infusion (see Pre-NDA meeting response). The Applicant selected excipients based on prior knowledge of various docetaxel formulations already on the market, except for the soy bean oil. Soy bean oil serves as a (b)(4) in this non-alcohol formulation. All selected excipients are presented in docetaxel injection at concentrations below the maximum amounts listed in the IIG for intravenous infusion (~~**Error! Reference source not found.**~~). The quality control specifications for excipients used in manufacturing docetaxel injection drug product are the same as those specified in the individual monographs.

The corrected section 2.3 Drug Formulation which replaces the previous version reads:

Docetaxel injection contains the same active ingredient as the LD but differs in the inactive ingredients (Table 1, Table 2, Table 3). The compositions of 3 strengths for docetaxel injection are presented in **Table 4**, including the excipients. The amount of polysorbate 80 in docetaxel injection is slightly higher than in the LD (b)(4)). The final concentration of polysorbate 80 in the diluted product (ready to infuse) is within the permissible limits of FDA's inactive ingredients guide (IIG) for intravenous infusion (see Pre-NDA meeting response). The Applicant selected excipients based on prior knowledge of various docetaxel formulations already on the market, except for the soy bean oil. Soy bean oil serves as a (b)(4) in this non-alcohol formulation. All selected excipients are presented in docetaxel injection at concentrations below the maximum amounts listed in the IIG for intravenous infusion **(Table 5)**. The quality control specifications for excipients used in manufacturing docetaxel injection drug product are the same as those specified in the individual monographs.

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/s/

WIMOLNUT MANHENG
11/20/2015

TODD R PALMBY
11/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 205934
Supporting document/s:	1
Applicant's letter date:	02/26/2015
CDER stamp date:	02/26/2015
Product:	Docetaxel injection, non-alcohol formula
Indication:	Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, head and neck cancer
Applicant:	Teikoku Pharma USA, Inc.
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	Wimolnut Manheng, PhD, DABT
Supervisor/Team Leader:	Todd R. Palmby, PhD
Division Director:	John Leighton, PhD, DABT (acting, DHOT) (Geoffrey Kim, MD DOP1)
Project Manager:	Sakar M. Wahby

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205934 are owned by Teikoku Pharma USA, Inc. or are data for which Teikoku Pharma USA, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 205934 that Teikoku Pharma USA, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205934.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

Docetaxel is a microtubule inhibitor that was approved by the US FDA 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. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cell.

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1.2 Brief Discussion of Nonclinical Findings

TPU relied upon the FDA's previous findings of safety and effectiveness for Taxotere as reflected in the drug's approved labeling. The Applicant was not required to perform any animal toxicology studies in support of the NDA submission for docetaxel injection. However, the Applicant included reports from three pharmacokinetic and toxicology studies in their NDA submission.

A GLP-compliant pharmacokinetic study comparing docetaxel injection and Taxotere in male Beagle dogs following an IV infusion dose of 0.75 mg/kg was conducted. Based on pharmacokinetic parameters in this study, docetaxel injection and Taxotere were determined to be comparable within a 95% confidence interval.

An in vitro, non-GLP, pharmacokinetic study comparing docetaxel protein binding to dog and human plasma between docetaxel injection and Taxotere was also submitted. Protein binding decreased in a concentration-dependent manner with both formulations (docetaxel injection vs Taxotere) over the concentration ranges evaluated (0.10-100 µg/mL). The protein binding values were similar for the two formulations in dog and human plasma.

A special toxicology study designed to assess complement activating (C3a and SC5b-9) potential of docetaxel injection compared to Taxotere in human serum at concentrations of 1 µg/mL to 100 µg/mL after 30 and 90 minute exposure times was conducted. There was no biologically significant difference in C3a mean concentrations across all time courses between docetaxel injection and Taxotere. However, mean concentrations of SC5b-9 observed with docetaxel injection were lower than Taxotere. The Applicant claims that docetaxel injection had less complement activation potential in SC5b-9 when compared to Taxotere.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, docetaxel injection may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

None

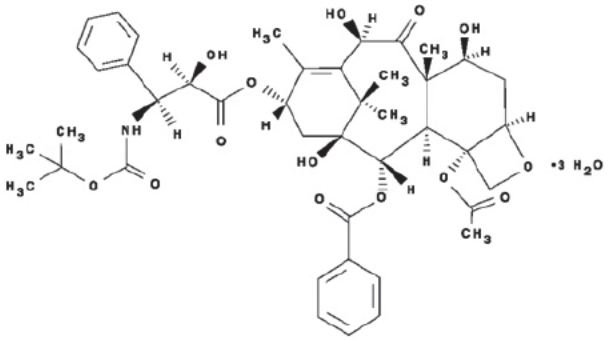
1.3.3 Labeling

No significant changes were made to the prescribing information in sections describing nonclinical information as compared to the LD.

2 Drug Information

2.1 Drug

CAS Registry Number:	148408-66-6
Generic Name:	Docetaxel
Code Name	TPU-004DO
Chemical Name:	(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl

	39 ester, 13-ester with 5β-20epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate
Molecular Formula:	$C_{43}H_{53}NO_{14}\cdot 3H_2O$
Molecular Weight:	861.93
Structure or Biochemical Description:	
Pharmacologic Class	Microtubule inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 020449 (Taxotere); DMF (b)(4), Type III DMF Number (b)(4), Type III DMF Number (b)(4), Type V DMF (b)(4), Type V DMF (b)(4)

2.3 Drug Formulation

Docetaxel injection contains the same active ingredient as the LD but differs in the inactive ingredients (Table 1, Table 2, Table 3). The compositions of 3 strengths for docetaxel injection are presented in **Error! Reference source not found.**, including the excipients. The amount of polysorbate 80 in docetaxel injection is slightly higher than in the LD (b)(4). The final concentration of polysorbate 80 in the diluted product (ready to infuse) is within the permissible limits of FDA's inactive ingredients guide (IIG) for intravenous infusion (see Pre-NDA meeting response). The Applicant selected excipients based on prior knowledge of various docetaxel formulations already on the market, except for the soy bean oil. Soy bean oil serves as a (b)(4) in this non-alcohol formulation. All selected excipients are presented in docetaxel injection at concentrations below the maximum amounts listed in the IIG for intravenous infusion (**Error! Reference source not found.**). The quality control specifications for excipients used in manufacturing docetaxel injection drug product are the same as those specified in the individual monographs.

Table 1: TPU's docetaxel injection formulation

Name	CAS Number	mg/mL
Docetaxel Trihydrate USP	148408-66-6	(b)(4)
Soybean Oil USP (b)(4)	(b)(4)	27.50
Polysorbate 80 NF	9005-65-6	(b)(4)
Polyethylene Glycol 300 NF	25322-68-3	
(b)(4) Citric Acid USP	(b)(4)	10.00
	Total:	(b)(4)

(b)(4)

[Excerpted from Applicant's Submission]

Table 2: Comparison of 20 mg vial of docetaxel injection and Taxotere

Ingredient	TPU (mg/mL)	One-vial Taxotere (mg/mL)
Docetaxel[1]	20.0	20
Soybean oil	27.5	N/A
Polysorbate 80	585.0	540
Polyethylene glycol 300	442.2	N/A
Citric acid, (b)(4)	10.0	N/A
Dehydrated alcohol	N/A	395

N/A = not applicable

(b)(4)

[Excerpted from Applicant's Submission]

Table 3: Proposed specifications for docetaxel injection drug product

Attribute	Test Method	Acceptance Criteria
Appearance	Visual	Clear, colorless to yellow viscous liquid, free of visible particles
Identification A (TLC)	USP Monograph for Docetaxel Injection, USP <201>	Meets the requirements
Identification B (HPLC)	USP Monograph for Docetaxel Injection	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
Assay	USP Monograph for Docetaxel Injection	90.0% – 110.0% of 20 mg/mL docetaxel
Organic impurities 10-Deacetyl baccatin 2-Debenzoxyl 2-pentenoyl docetaxel Docetaxel Crotonaldehyde analog 6-Oxodocetaxel 4-Epidocetaxel 4-Epi-6-oxodocetaxel Any unspecified impurity Total impurities	USP Monograph for Docetaxel Injection	 NMT 0.30% — — NMT 1.3% NMT 1.5% NMT 1.0% NMT 0.5% NMT 0.2% NMT 3.5%
Extractable volume	USP <1>	20 mg/1 mL: NLT (b) (4) 80 mg/4 mL: NLT 160 mg/8 mL: NL'
Bacterial endotoxins	USP Monograph for Docetaxel Injection, USP <85>	It contains NMT 1.94 USP Endotoxin Units/mg of docetaxel (anhydrous)
Sterility	USP Monograph for Docetaxel Injection, USP <71>	Negative for growth
Particulate matter in injections	USP Monograph for Docetaxel Injection USP <788>, Method 2	(b) (4) NMT (b) (4) /container NMT ontainer

NLT = not less than
NMT = not more than

[Excerpted from Applicant's Submission]

Table 4: Composition of docetaxel injection with 3 strengths formulation

Component	Function	Quality Standard	Quantity (mg)			
			Per mL	Per 1 mL/ 2 mL Vial	Per 4 mL/ 8 mL Vial	Per 8 mL/ 10 mL Vial
Docetaxel[1]	Active	USP, EP	20.0	20.0	80.0	160.0
(b)(4) soybean oil	(b)(4)	USP, EP	27.5	27.5	110.0	220.0
Polysorbate 80		NF, EP, JP	585.0	585.0	2340.0	4680.0
Polyethylene glycol 300		NF, EP, JPE	442.2	442.2	(b)(4)	
Citric acid, (b)(4)		USP, EP, JP	10.0	10.0	40.0	80.0
(b)(4)		NF	N/A	N/A	N/A	N/A
		Total	1084.7	1084.7	(b)(4)	

EP = European Pharmacopoeia
JP = Japanese Pharmacopoeia
JPE = Japanese Pharmaceutical Excipients
NF = National Formulary
USP = United States Pharmacopeia

(b)(4)

[Excerpted from Applicant's Submission]

Table 5: Excipients in docetaxel injection and maximum amount listed in the Agency's Inactive Ingredients Guideline Data base (IIG)

Excipient	Route of Administration	IID Limit (%)	Concentration in Docetaxel Infusion Solution (%)
Soybean oil	IV; Injection	≤ 10	(b)(4)
Polysorbate 80	IV; Injection	≤ 50	
Polyethylene glycol 300	IV; Injection	≤ 65	
Citric acid, (b)(4)	IV; Injection	≤ 0.4	

IID = Inactive Ingredients Database
IV = intravenous

[Excerpted from Applicant's Submission]

2.4 Comments on Novel Excipients

There are no novel excipients used in the manufacturing of docetaxel injection.

2.5 Comments on Impurities/Degradants of Concern

The specifications for impurities in the drug substance are acceptable from a Pharmacology/Toxicology perspective as they comply with established specifications in the USP monograph for docetaxel (Table 6).

Table 7 presents the impurities identified in docetaxel injection drug product. The only new degradation product observed at a concentration above (b) (4) % (unspecified impurity) is identified as an (b)(4). The (b)(4) was observed above the USP specification limit ((b)(4)) at the 6 month time point under accelerated storage condition (40°C). However, it was not observed above the specification limit release at long-term, or intermediate storage conditions (25°C and 30°C, respectively) at 12 months, or at accelerated storage conditions (40°C) at 4 months. Structural analysis of the impurity showed that it has an approximate molecular weight of (b) (4), is similar to the known (b) (4) impurity, and lack of (b)(4). The CMC reviewer concurs that the impurity is only observed at the (b)(4) and the Applicant only plans to store the drug product at room temperature (20-25°C) condition. In addition, the specification for impurities in the drug product complies with established specification in the USP monograph for docetaxel trihydrate. Therefore they are acceptable from a Pharmacology/Toxicology perspective (Table 8).

Table 6: Tests and justifications for the proposed specification for docetaxel injection drug substance

Attribute		Justification
Appearance: white or almost white crystalline powder		Supported by (b)(4) (b)(4)
Solubility: Freely soluble in acetone; soluble in methanol; practically insoluble in water		Based on ICH Q6A and EP 2.2.1, supported by (b)(4) (b)(4)
Specific optical rotation $[\alpha]_D^{20}$: -39° to -41°, calculated on the anhydrous and solvent-free basis		Based on USP Monograph , supported by (b)(4) (b)(4)
Identification	IR: the infrared absorption spectrum of the sample should correspond to the spectrum of the docetaxel reference substance	Based on USP Monograph
	HPLC: the retention time of the major peak of the Sample Solution corresponds to that of the Standard Solution, as obtained in the Assay	
Appearance of solution	Clarity of solution: Not more opalescent than reference suspension II	Based on ICH Q6A and EP 2.2.1, supported by (b)(4) (b)(4)
	Color of solution: Not more intensely colored than reference solution B_5	
Heavy metals: NMT 20 ppm		Based on USP Monograph, supported by (b)(4)
Water: 5.0% – 7.0%		Based on ICH Q6A and USP <921> Method Ia, supported by (b)(4) (b)(4)
Residue on ignition: NMT 0.1%		Based on USP Monograph, supported by (b)(4)

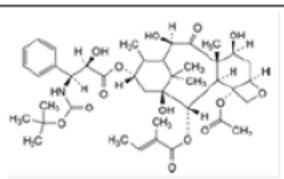
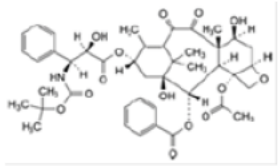
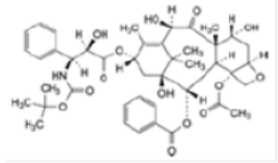
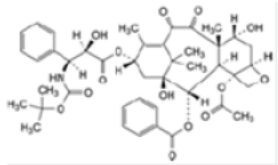
[Excerpted from Applicant's Submission]

Tests and justifications for the proposed specification for docetaxel injection drug substance (Continued)

Attribute			Justification
Organic impurities (HPLC)	10-Deacetylbaccatin: 2-Debenzoxyl 2pentenoyl docetaxel: 6-Oxodocetaxel: 4-Epidocetaxel: 4-Epi-6-oxodocetaxel: Any unspecified impurity: Total impurities:	NMT 0.15% NMT 0.5% NMT 0.3% NMT 0.3% NMT 0.2% NMT 0.10% NMT 1.0%	Based on USP Monograph, (b)(4)
(b)(4)			Based on ICH Q3C and USP <467>, supported by (b)(4) (b)(4) (b)(4) (USP <621> and EP 2.2.28)
Assay (HPLC): Contains 97.5% to 102.0% of docetaxel ($C_{43}H_{53}NO_{14}$), calculated on the anhydrous and solvent-free basis			Based on USP Monograph and (b)(4)
Bacterial endotoxins: Less than 0.4% EU/mg			
Microbial limits	Total aerobic microbial count: NMT (b) (4) CFU/g		
	Total molds and yeasts count: NMT 10 CFU/g		

[Excerpted from Applicant's Submission]

Table 7: Characterization of impurities for docetaxel injection drug product

Impurity	Structure	Origin
2-Debenzoyl 2-pentenoyl docetaxel (Impurity A)		(b)(4)
6-Oxodocetaxel (Impurity B)		
4-Epidocetaxel (Impurity C)		
4-Epi-6-oxodocetaxel (Impurity D)		
Crotonaldehyde analog		
(b)(4)		

RRT = relative retention time

[Excerpted from Applicant's Submission]

Table 8: Specification of docetaxel injection drug product

Attribute	Test Method	Acceptance Criteria
Appearance	Visual	Clear, colorless to yellow viscous liquid, free of visible particles
Identification A (TLC)	USP Monograph for Docetaxel Injection, USP <201>	Meets the requirements
Identification B (HPLC)	USP Monograph for Docetaxel Injection	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
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Particulate matter in injections	USP Monograph for Docetaxel Injection USP <788>, Method 2	(b) (4) NMT (b) (4) container NMT container

NLT = not less than
NMT = not more than

[Excerpted from Applicant's Submission]

2.6 Proposed Clinical Population and Dosing Regimen

TPU proposed dosing regimen is consistent with current Taxotere labeling for the treatment of breast cancer (BC), non-small cell lung cancer (NSCLC), hormone refractory prostate cancer (HRPC), gastric adenocarcinoma (GC), and squamous cell carcinoma of the head and neck cancer (SCCHN). The recommended dose for treatment of BC is 60 mg/m^2 to 100 mg/m^2 infused intravenously over 1 hour every 3

weeks. The recommended dose for NSCLC, GC and SCCHNA is 75 mg/m^2 infused intravenously over 1 hour every 3 weeks.

2.7 Regulatory Background

The Applicant submitted NDA 205934, 505 (b)(2) marketing application for docetaxel injection on February 26, 2015 after addressing items recommended in the pre-NDA meetings on August 19, 2014 and October 15, 2014. A pre-NDA meeting was granted on Jul 15, 2014 for discussing the product development plan for a 505 (b)(2) application for docetaxel injection. The applicant also submitted an amendment to updated labeling on June 1, 2015 following filing review issues concerning the prescribing information identified in the filing communication dated May 11, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	eCTD Module
Protein binding study comparison between Teikoku docetaxel formulation (TPU-004DO) and Taxotere ® in dog and human plasma by equilibrium dialysis (Study # MC14M-0005)	4.2.2.3
Complement activation comparison of Teikoku docetaxel formulation (TPU-004DO) and Taxotere ® in human serum (Study # 743578)	4.2.3.7.7
Comparison of the pharmacokinetic profiles of docetaxel formulation and Taxotere ® in Beagle dogs (Study #8296738)	4.2.3.7.7

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No new pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No ADME study reports were submitted. TPU submitted a non-GLP protein binding study comparing the docetaxel injection formulation and Taxotere in the final infusion solution in dog and human plasma (study MC14M-0005, eCTD 4.2.2.3). The plasma protein binding study was conducted to provide additional information that indicates whether the difference in inactive ingredients might affect the distribution or elimination of docetaxel injection. In addition, TPU also submitted a report from a single-dose pharmacokinetic study comparing docetaxel injection and Taxotere administered by IV infusion in beagle dogs (study 8296738, eCTD 4.2.3.7.7).

- The protein binding was determined by using rapid equilibrium dialysis (RED). Dog and human plasma samples were individually spiked with the two formulations of docetaxel at 0.100, 1.00, 3.00, 10.0 and 100 µg/mL. Over the concentration ranges evaluated, docetaxel protein binding decreased as the concentration increased for both docetaxel injection and Taxotere, indicating a concentration-dependent change in the binding. Based on the results, the protein binding values were similar for the two formulations in dog and human plasma (Table 9).

Table 9: Summary of docetaxel plasma protein binding results

Species	Target Concentration (µg/mL)	%Bound (Mean ± SD)	
		TPU-004DO	Taxotere®
Dog	0.100	93.5 ± 0.737	92.6 ± 0.902
	1.00	92.6 ± 0.451	90.6 ± 1.28
	3.00	92.8 ± 0.361	91.1 ± 0.0577
	10.0	92.4 ± 0.529	90.4 ± 2.03
	100	86.7 ± 1.06	85.1 ± 1.44
Human	0.100	96.3 ± 0.458	95.0 ± 0.493
	1.00	96.3 ± 0.173	95.9 ± 0.141
	3.00	95.6 ± 0.265	95.0 ± 0.702
	10.0	93.2 ± 1.65	94.2 ± 1.01
	100	91.8 ± 0.907	93.1 ± 0.781

(Excerpted from Applicant's submission)

- The PK of docetaxel injection was compared to that of Taxotere in male Beagle dogs in a cross over design to determine pharmacokinetic comparability (Table 10). Dogs were administered a single IV infusion dose (0.75 mg/kg) of each formulation over approximately 1 hr. The PK study was conducted according to

US GLP for non-clinical laboratory analysis with the following exceptions: the final diluted dose formulations did not undergo GLP stability analysis or dose analysis and the study statistician had not completed GLP training prior to conducting the statistical analysis. The Applicant claims that these deviations do not impact the integrity of the study. For each phase, blood samples were collected from a jugular vein at 2, 4, 6, 8, 12 and 24 hour postdose. The results demonstrated that PK parameters were similar between the two formulations. Similar volume of distribution results suggest that docetaxel is highly distributed to the tissue after IV infusion of both the docetaxel injection and Taxotere (Table 11). The maximum plasma concentration (C_{max}) and the area under the curve from time 0 to the last measurable time point (AUC_{0-t}) ratio were close to 100% and entirely contained within the 80 to 125 percentile window, indicating that the formulations are bioequivalent within a 95% confidence interval in dogs (Table 12).

Table 10: Study design for PK study

Study Design

Phase/ Group	Number of Male Animals	Test Article	Dose Route	Target Dose Level (mg/kg)	Target Dose Concentration (mg/mL)	Target Dose Volume (mL/kg)
1/1	6[a]	Taxotere®	IV	0.75	0.5	1.5
1/2	6[a]	Docetaxel Formulation	IV	0.75	0.5	1.5
2/1	6	Docetaxel Formulation	IV	0.75	0.5	1.5
2/2	6	Taxotere®	IV	0.75	0.5	1.5

IV Intravenous; administered as an approximately 1-hour infusion.

Notes: There was a 21- or 22-day, as applicable, washout period between phases.
An extra animal was used as a replacement for Phase 1 (due to a misdose/incomplete dose).
See "Medicant Administration" section for details specific to predose and postdose treatments.

a For Phase 1, one animal per group was dosed one day in advance of the remaining animals to assess tolerability. Group 1 Animal No. H04183 and Group 2 Animal No. H04189 were dosed on 10 February 2014; the remaining 5 animals per group were dosed on 11 February 2014.

[Excerpted from the Applicant's submission]

Table 11: Summary of PK results comparing docetaxel injection and Taxotere

Test Article	Dose Level (mg/kg)		C_{max} (ng/mL)	AUC_{0-t} (ng·hr/mL)	CL (mL/hr/kg)	V_{ss} (mL/kg)	V_z (mL/kg)
Docetaxel Formulation (TPU-004DO)	0.75	Mean	369	531	1310	8660	38300
		SD	66.9	90.0	156	6000	18400
		N	12	12	7	7	7
Taxotere®	0.75	Mean	366	547	1270	11200	45400
		SD	100	134	227	9910	24400
		N	12	12	6	6	6

CL Clearance
V_{ss} Volume of distribution at steady state.
V_z Volume of distribution during the terminal phase.
Note: Due to the lack of a distinct elimination phase, estimation of elimination phase half-life ($t_{1/2}$) was calculated based on approximately half of the animals.

[Excerpted from the Applicant's submission]

Table 12: Summary of mean PK parameters (C_{max} and AUC)

Parameter (unit)	N	LS Mean 0.75 mg/kg Docetaxel (Test)[a]	N	LS Mean 0.75 mg/kg Docetaxel (Reference)[b]	Test/ Reference (%)	95% Confidence Interval (%)
C_{max} (ng/mL)	12	364	12	354	103	(88.1, 120)
AUC_{0-inf} (ng·hr/mL)[c]	7	571	6	591	96.6	(77.5, 120)
AUC_{0-t} (ng·hr/mL)	12	524	12	533	98.4	(87.6, 111)

LS Least squares.
a Docetaxel Formulation.
b Taxotere®.
c AUC_{0-inf} statistical comparisons should be interpreted cautiously as the parameters could not be calculated for all animals.

[Excerpted from the Applicant's submission]

6 General Toxicology

Not submitted

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

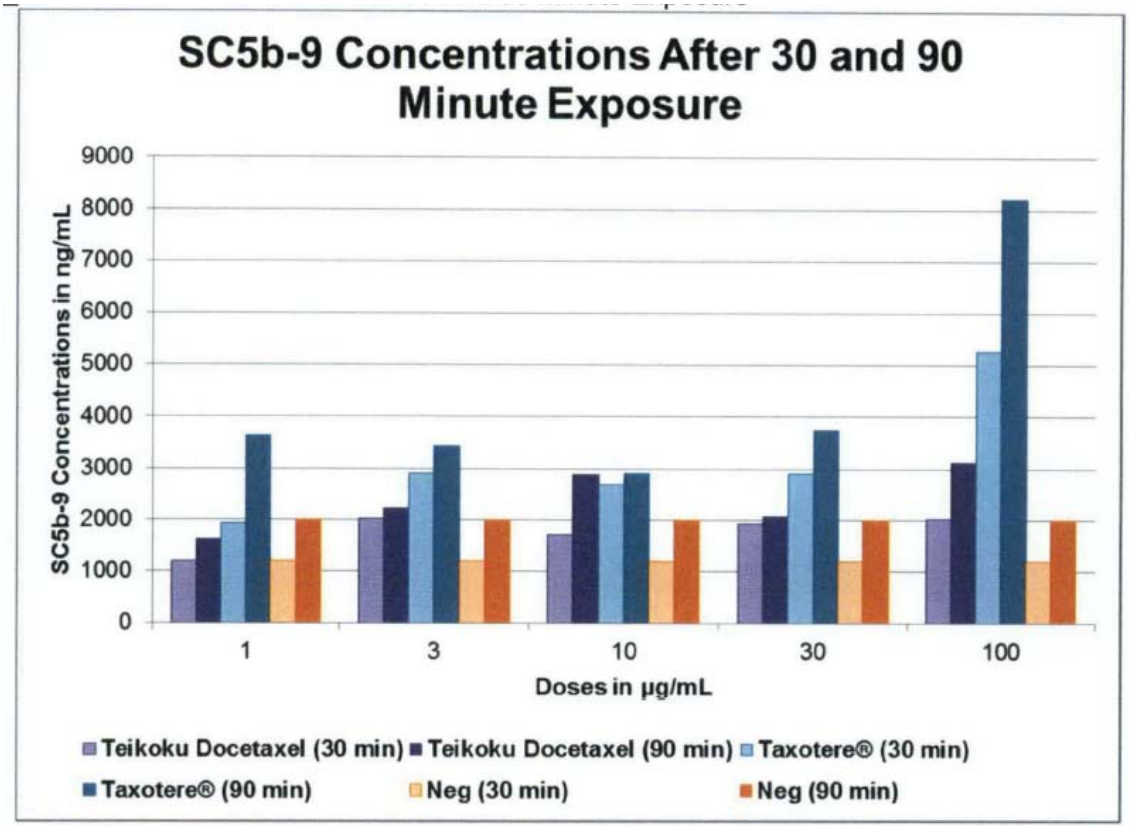
9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

A GLP-compliant, in vitro evaluation of the complement activating potential of docetaxel injection compared to Taxotere was examined in human serum at 5 concentrations (1, 3, 10, 30 and 100 µg/mL) of both formulations (n =3). The exposed serum was then evaluated for activation using commercially prepared enzyme immunoassay kits that detect the presence of specific complement proteins: C3a and SC5b-9. Docetaxel injection resulted in similar C3a levels as Taxotere. Thus, the compliment activation potential for docetaxel injection and Taxotere appear comparable based on C3a. The SC5b-9 levels resulting from docetaxel injection in general were lower than for Taxotere. Statistically significant differences in SC5b-9 levels were observed at the 1 and 100 µg/mL concentrations for both 30 and 90 minutes and at 30 µg/mL for the 90 minute exposure time. This suggests that docetaxel injection may result in less immunogenic potential when compared to Taxotere based on SC5b-9 (Figure 1).

Figure 1 SC5b-9 concentrations after 30 and 90 minute exposure



(Excerpted from Applicant's submission)

11 Integrated Summary and Safety Evaluation

In vitro protein binding was examined in dog and human plasma using RED analysis. Plasma samples were individually spiked with the two formulations of docetaxel at 0.100, 1.00, 3.00, 10.0 and 100 µg/mL. There was a concentration-dependent change in the binding of docetaxel to proteins in dog and human plasma for both formulations. Docetaxel protein binding decreased as the concentration increased for both docetaxel injection and Taxotere. Based on the results, the protein binding values were similar for the two formulations in dog and human plasma.

TPU also submitted results from a GLP-compliant, single dose (0.75 mg/kg) PK study in male beagle dogs (n=6) comparing the pharmacokinetics of docetaxel injection to the LD. After a single IV infusion dose of each formulation, in general, docetaxel levels declined in a multi-exponential manner and the PK parameters (C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, CL, V_{ss} and V_z) were similar between the 2 formulations. However, there was a 27.7% difference in the mean $t_{1/2}$ values (19.8 vs 25.3 hours of docetaxel injection and LD, respectively) and a 29.3% difference in the mean V_{ss} (8660 vs 11200 mL/kg of docetaxel injection and LD, respectively). These results suggest the potential that docetaxel injection may have a higher distribution to tissues after IV infusion when compared to the LD, but these values were not biologically significant.

In addition, a GLP-compliant study was conducted to determine concentrations of C3a and SC5b-9 in human serum following exposure to either docetaxel injection or Taxotere at 5 concentrations (1-100µg/mL) for 2 time points (30 and 90 minutes, n=3) in vitro. Based on C3a mean concentration and time course, there was no biologically significant difference between docetaxel injection and Taxotere. However, there was a significant difference in SC5b-9 mean concentrations with a dose-response. In summary, results of this in vitro assay suggest docetaxel injection may result in less complement activation compared to Taxotere.

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/s/

WIMOLNUT MANHENG
10/21/2015

TODD R PALMBY
10/22/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 205934 **Applicant:** Keikoku Pharma USA, Inc. **Stamp Date:** 02/26/2015

Drug Name: Docetaxel injection [redacted](b)(4), non-alcohol formula **NDA Type:** 505(b)(2)

On **initial** overview of the NDA for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	✓		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	✓		The Applicant is relying on the FDA's previous finding of safety and efficacy for Taxotere.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	✓		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	✓		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	✓		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	✓		The Applicant's proposed labeling will be reviewed during the NDA review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	✓		Acceptability of the Applicant's proposed specifications will be determined during the NDA review.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wimolnut Manheng, Ph.D., DABT	04/21/2015
Reviewing Toxicologist	Date
Todd R. Palmby, PhD	04/21/2015
Team Leader	Date

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/s/

WIMOLNUT MANHENG
04/21/2015

TODD R PALMBY
04/21/2015