CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205934Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 205934
Review #2
Review Date: 22-Dec-2015

Drug Name/Dosage Form	Docetaxel/ Injection, Solution,
Strength	20 mg/mL; 80 mg/4mL; 160 mg/8 mL
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Teikoku Pharma USA, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
	February 26, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	Branch I/New Drug API Division (ONDP)
Drug Product	Rajiv Agarwal	Branch II/Division I (ONDP)
Process	Vidya Pai	Branch VII/Division III (OPF)
Microbiology	Nandini Bhattacharya	CDER/OPQ/OPF/DMA/MABII
Facility	Wayne Seifert	Branch 1/Division V (OPF)
Biopharmaceutics	Jing Li	Division of Biopharmaceutics
Business Process Manager	Rabiya Laiq	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Xiao Hong Chen	Branch II/Division I (ONDP)
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)*	Rajiv Agarwal	Branch II/Division I (ONDP)

* Teikoku Pharma USA, Inc. (TPU) claims a categorical exclusion from the requirement of an Environmental Assessment for Docetaxel Injection Non-Alcohol Formula under 21 CFR §25.31(a) on the basis that the drug product is not expected to increase the use of the active moiety, and also under 21 CFR §25.31(b) on the basis that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant (although derived from cultivated plants**) and/or animal material 21 CFR 25 21(b). ***Granted.***

(b)(4)

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Docetaxel Trihydrate	Adequate	16-OCT-2015	The DMF review will be entered in DARRTS soon. API Reviewer: Haripada Sarker
	Type III		(b) (4)	Adequate	2-MAY-2015	Dr. Martin Haber
	Type III			Adequate	28-FEB-2014	Dr. Edwin Jao
	Type III			Adequate	09-APR-2015	Dr. Nutal Mytle

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Taxotere	NDA 020449	Listed Drug

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for Approval. Overall manufacturing inspection recommendation is "Approval" provided by the facility reviewer, Wayne Seifert, on December 21, 2015. Product quality review of this NDA has no outstanding deficiencies or other review issues, and recommended "Acceptable" for the NDA. Refer to the Integrated Assessment of Quality review #1 in Panorama.

In the action letter, please include the following statement:

An expiry of 24 months was granted for Docetaxel Injection stored at 20-25°C, with excursions permitted between 15-30°C.

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

N/A.

II. Summary of Quality Assessments

This review is an addendum for a final overall recommendation for pre-approval inspection of this NDA. In the 10/05/2015 facility review conducted by Wayne Seifert, a final facilities recommendation was not made because a compliance decision was still pending for the AMRI Burlington, Inc. site (FEI 3002951540) proposed for drug product manufacture. A compliance decision of approve has now been rendered for the AMRI Burlington Inc. site. The status of the AMRI Burlington, Inc. site with respect to this application has been changed from OAI to VAI for PAI. All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint. Refer to Wayne Seifert's review dated December 21, 2015 in panorama.

Application Technical Lead Signature: The NDA is recommended for Approval. Overall manufacturing inspection recommendation is "Approval" provided on December 21, 2015. Product quality review of this NDA has no outstanding deficiencies or other review issues, and recommended "Acceptable" for the NDA.

Xiao Hong Chen, Ph.D.
Acting Quality Assessment Lead
OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII

Xiaohong Chen -A

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Date: 2015.12.22 09:57:59 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51,10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 12/21/2015
To: Administrative File, STN 205934/0
From: Wayne Seifert, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Mike Shanks, Acting Branch Chief, Branch 1, CDER/OPQ/OPF/DIA
Subject: Original NDA
US License: Pending
Applicant: Teikoku Pharma USA, Inc..
Mfg Facility: Drug Substance: (b)(4)
Drug Product: AMRI Burlington , Inc. (FEI 3002951540)
Product: Docetaxel Injection (b)(4) Non-Alcohol Formula
Dosage: Injection, Solution, 20 mg/ml; 80 mg/4 ml; 160 mg/8 ml, Intravenous Infusion
Indication: Breat Cancer, Non-Small Cell Lung Cancer, Hormone Refractory Prostate Cancer, Gastric Adenocarcinoma and Squamous Cell Carcinoma of the Head and Neck Cancer.
Due Date: 12/26/2015

RECOMMENDATION: The application is recommended for approval from a facilities assessment standpoint.

SUMMARY

This assessment is an addendum for a 10/05/2015 facilities review of NDA 205934 located in SharePoint. In the 10/05/2015 review, a final facilities recommendation was not made because a compliance decision was still pending for the AMRI Burlington, Inc. site (FEI 3002951540) proposed for DP manufacture. A compliance decision of approve has now been rendered for the AMRI Burlington Inc. site. All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint.

ASSESSMENT

An assessment of the proposed DS and DP manufacturing and testing sites for the subject NDA was presented in the 10/05/2015 facilities review. A final facilities recommendation was not rendered in that review, because of a pending PAI compliance review for the proposed DP

manufacturing site, AMRI Burlington, Inc. The status of the AMRI Burlington, Inc. site with respect to this application is now known and is summarized below:

- AMRI Burlington, Inc. 99 South Bedford St., Burlington MA 01803 (FEI 3002951540). On 12/21/2015, CDER/OPF/DIA and DO rendered an approve decision for a PAI conducted 08/10-19/2015 to assess Docetaxel Injection (b)(4), Non-Alcohol Formula DP manufacture at this facility. This pre-approval inspection of a drug manufacturer was conducted in accordance with CP 7346.832 "NDA Pre-Approval Inspections/Methods Validation" for profile (b) (4) Currently, the firm only distributes clinical supply; the firm does not distribute any commercial products. Quality, Production, Materials, Facilities and Equipment, and Laboratory Controls System were covered. The original classification was OAI for PAI, with a recommendation of withhold. The classification is downgraded to VAI for PAI based on the firm's response.

CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

Wayne E. Seifert -S

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Date: 2015.12.21 11:04:07 -05'00'

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Michael R. Shanks -S

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Date: 2015.12.21 11:27:03 -05'00'

Mike Shanks
Microbiologist and Acting Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Recommendation: Pending the overall recommendation for pre-approval inspection for the facilities

NDA 205934
Review #1
Review Date: 16-Oct-2015

Drug Name/Dosage Form	Docetaxel/ Injection, Solution,
Strength	20 mg/mL; 80 mg/4mL; 160 mg/8 mL
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Teikoku Pharma USA, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
	February 26, 2015

Quality Review Team

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Environmental Assessment (EA)*	Rajiv Agarwal	Branch II/Division I (ONDP)

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(b)(4)

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Quality Review Data Sheet

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2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
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	Type III			Adequate	28-FEB-2014	Dr. Edwin Jao
	Type III			Adequate	09-APR-2015	Dr. Nutal Mytle

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Taxotere	NDA 020449	Listed Drug

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Final recommendation is still pending. As of 10/16/2015, the drug product facility assessment is still pending for AMRI Burlington, Inc. FEI 3002951540. A Prior Approval and GMP Inspection was conducted 8/10 – 19/2015, with a compliance review pending. The inspection report and any applicable form response will be reviewed before an overall recommendation can be made. The completed Overall Facility Assessment will be provided as an addendum to this review at a later date.

Product quality review of this NDA has no outstanding deficiencies or other review issues, and recommended "Acceptable" for the NDA.

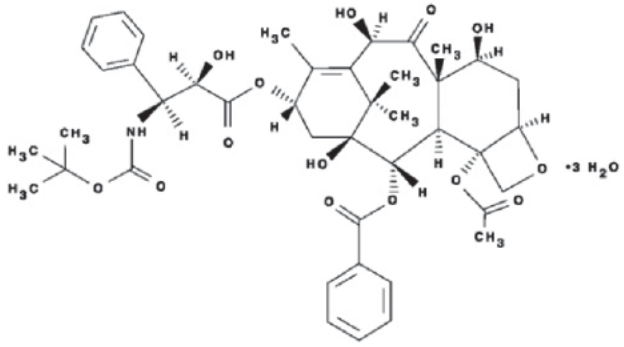
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

The NDA was filed as a 505(b)(2) application, using Taxotere (NDA 020449) as the listed drug (LD). This drug product is a parenteral solution for IV administration and has the same active ingredient, route of administration, dosage form, and indications as the LD, but contains different inactive ingredients. The drug product is a non-alcohol formulation of Docetaxel Injection. The applicant has requested a waiver of the in vivo bioequivalence study, which was deemed to be acceptable.

Throughout the review document, both Docetaxel Injection and Docetaxel Injection (b) (4) have been used interchangeably. The established name for the drug product is Docetaxel Injection. The applicant initially proposed the drug product established name as Docetaxel Injection (b) (4) The Docetaxel Injection in this NDA is a single vial formulation, no prior dilution with a diluent and is ready to add to the infusion solution, consisting of 0.9% Sodium Chloride solution or 5% Dextrose solution to product a final concentration of 0.3 mg/mL to 0.74 mg/mL. Therefore, the word (b)(4) has been deleted from the drug product established name.

A. Drug Substance [Docetaxel] Quality Summary



- Docetaxel Trihydrate
- $C_{43}H_{53}NO_{14} \cdot 3H_2O$
- MW: 861.93 (trihydrate)
- MW: 807.88 (anhydrate)
- CAS registry #: 148408-66-6
- white or almost white crystalline powder
- Practically insoluble in water, freely soluble in acetone, soluble in methanol
- Melting point: 200°C
- Store preserved in tight container, protected from light [redacted](b)(4)

IUPAC Name: 1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}, trihydrate

Docetaxel trihydrate USP, manufactured by [redacted](b)(4) is the active ingredient in Docetaxel Injection, Non-Alcohol Formula. It is a microtubule inhibitor, belonging to the taxoid family and is indicated for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer. It is manufactured by [redacted](b)(4) using the starting material, [redacted](b)(4) [redacted](b)(4) It is stored in a [redacted](b)(4) The specification for docetaxel trihydrate complies with the USP monograph. Batch analysis data for the three exhibit batches were provided in the NDA, which conform to the specification. Three consecutive exhibit batches of docetaxel trihydrate USP manufactured at the production scale of approximately [redacted](b)(4) have been placed on stability study; and sufficient stability data were submitted to support the [redacted](b)(4) months retest date, which was deemed to be acceptable. Stress testing data demonstrate that the drug substance is stable under the conditions of light, humidity, oxidation, and hydrolysis. Significant degradation of the drug substance has been observed under the stress conditions of acid, alkali, and high temperature. Detailed complete information regarding the characterization, manufacturing and controls for docetaxel trihydrate drug substance is provided in DMF No. [redacted](b)(4)

B. Drug Product [Docetaxel Injection] Quality Summary

Docetaxel Injection, manufactured by Teikoku Pharma USA (TPU), is a non-alcohol formulation of for IV administration. Docetaxel Injection is available in [redacted](b) (4) 80 mg/4 mL and 160 mg/8 mL multi-use vials. Each mL contains 20 mg docetaxel. The preparation and administration of Docetaxel Injection, Non-Alcohol Formula is the same as the listed drug, Taxotere®. Docetaxel Injection is diluted by injecting the drug product 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. Docetaxel diluted solution at the above concentration range is physicochemically stable when stored at room temperature for 24 hours.

The container closure system consists of Type 1 clear glass vials capped with (b)(4) rubber stoppers and aluminum flip-off seals. The vials are packed in the cartons as secondary packaging system, to protect from the exposure of light as docetaxel is slightly light sensitive. Due to the viscous nature of the product caused by the two (b)(4) applicant targets presentations with excess fill volumes as recommended per USP<1151> for viscous liquids. For the three strength of Docetaxel Injection, 20 mg/mL, 80 mg/mL, and 160 mg/mL that are contained in vials with three different sizes, 2 mL, 8 mL, and 19 mL, the fill volumes are (b)(4) mL, (b)(4) mL and (b)(4) mL, respectively.

Docetaxel Injection contains the following compendial excipients, soybean oil, polysorbate 80, polyethylene glycol (PEG) 300, citric acid, (b)(4) (b)(4). All excipients used in the drug product formulation comply with the USP/NF compendial monographs. Soybean oil serves as a (b)(4) in this non-alcohol formulation. Soybean oil (b) (4) docetaxel (b) (4) when diluted in 0.9% Sodium Chloride solution and 5% Dextrose solution for IV administration. Polysorbate 80 was chosen due to its use in all marketed docetaxel injection products. Polysorbate 80 serves as a (b) (4) . Citric acid is used to (b)(4) of the formulation.

The sterilization method for Docetaxel Injection uses (b)(4) of Docetaxel trihydrate. The proposed manufacturing process for Docetaxel Injection consists of the following key manufacturing steps: (b)(4) (b)(4) filled across 3 different vial presentations ((b)(4) into 2 mL vials; (b)(4) into 8 mL vials; and (b)(4) into 10mL vials). The manufacturing process has been appropriately validated.

Specification for Docetaxel Injection is consistent with the USP Monograph for Docetaxel Injection, and is in accordance with the ICH Q3B(R) guidance. The registration batches of Docetaxel Injection were manufactured and released by AMRI Burlington, Inc. in accordance with their release specification.

Stability data demonstrated that Docetaxel Injection is stable when stored at long term 25°C/60% RH for 18 months and intermediate (30°C/65%RH) storage conditions for 12 months. Based on stability data and ICH QIE guidelines, an *expiry of 24 months* was granted for Docetaxel Injection stored at 20-25°C, with excursions permitted between 15-30°C. The drug product is designated for (b) (4); a puncture study was performed to provide data in support of the stability and integrity of the multi-use container to prevent microbial contamination.

As of the date of this review, the NDC# is still pending. The applicant states that they will need more time to amend the container/closure labels and PI with the NDC#, which would still be before the PDUFA date. Per 21 CFR 201.2 , the NDC number is requested but not required on all drug labels and in all drug labeling. Since labeling negotiations are on-going and labeling will not be finalized until closer to the PDUFA date of December 2015, it is reasonable to grant the applicant's request to provide the NDC #s within their suggested timeframe.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Taxotere
Non Proprietary Name of the Drug Product	Docetaxel Injection
Non Proprietary Name of the Drug Substance	Docetaxel
Proposed Indication(s) including Intended Patient Population	Breast cancer, non-small cell lung cancer (NSCLC), hormone refractory prostate cancer (HRPC), gastric adenocarcinoma (GC), squamous cell carcinoma of the head and neck cancer.
Duration of Treatment	Varies. Refer to Package Insert.
Maximum Daily Dose	100 mg/m^2
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: Based on the literature, docetaxel is likely to be a BCS class IV drug.
   - Drug Product: N/A. The drug product is a solution for injection.

2. Biowaivers/Biostudies
   - Biowaiver Requests: The biowaiver request is granted on the basis of the comparable physical characteristics of the (b)(4) to the listed drug and the solubility behavior of the active ingredient in the solution for intravenous use.
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches N/A.

F. **Any Special Product Quality Labeling Recommendations** N/A.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Final recommendation is still pending due to pending overall recommendation for pre-approval inspection for the manufacturing facilities.

Xiao Hong Chen, Ph.D.
Acting Quality Assessment Lead
OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII

Xiaohong Chen -S

Digitally signed by Xiaohong Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaohong Chen -S, 0.9.2342.19200300.100.1.1=1300133168
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21. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

The drug product is a solution for intravenous infusion and therefore dissolution testing is not applicable.

The NDA was filed as a 505(b)(2) application, using Taxotere (NDA 020449) as the listed drug (LD). This drug product has the same active ingredient, route of administration, dosage form, and indications as the LD, but contains three different inactive ingredients. In particular, the drug product does not contain alcohol but contains soybean oil, PEG 300, and citric acid which are not present in the LD. The Applicant is requesting a waiver of the in vivo bioequivalence study. The review is focused on evaluating the adequacy of the data submitted to support the biowaiver request.

Regulatory History:

The reference product, Taxotere, was initially approved on May 14, 1996, as a 2-vial drug product with one vial for Docetaxel Injection and the other for the Diluent. The 1-vial formulation of Taxotere, which is referenced by the current application, was approved on August 2, 2010.

There have been 7 approved 505 b(2) drug products that referenced Taxotere (either 1 or 2-vial formulations). None of the NDAs contains exactly the same inactive ingredients as the formulation of Taxotere, except for NDA 022534, which used the same excipients but in lower quantities.

Biowaivers were granted for all of the 7 NDAs, largely based on 21 CFR 320.22(b)(1) regulations and the solubility property of parenteral solutions. A few NDAs provided information to demonstrate that the differences in inactive ingredients do not impact the properties of the drug product, such as, osmolality, pH, (b) (4). Below are three of the examples:

- NDA 203551: The drug product is a 1-vial formulation referencing the 2-vial Taxotere. The drug product contains citric acid and Povidone in addition to the excipients contained in Taxotere. The NDA provided osmolality comparison and the data showed that the osmolality of their product doubles that of the 2-vial Taxotere, but is comparable to that of the 1-vial Taxotere. Therefore the biowaiver request was granted.
- NDA 022312: The drug product is a 2-vial formulation, and contains PEG-300 in addition to the excipients contained in Taxotere. Comparison of pH values was provided, but the pH of the diluted solution of the drug product is slightly (b)(4) than that of Taxotere in both (b)(4). As the differences in pHs are not expected to significantly affect the amount of drug delivered, the biowaiver request was granted.

- NDA 202356: It is a 1-vial drug product and contains PEG and EDTA as additional inactive ingredients. The drug product showed comparable [redacted] size in diluted solution and comparable drug release from the [redacted] solutions. In addition, BE in an animal model and comparable plasma protein binding in vitro further supported similarity. Biowaiver was granted.

Drug Product Formulation

A comparison of TPU's formulation vs. One-vial Taxotere (LD) is provided in Table 33-1.

Table 33-1. Formulation Comparison- TPU Formulation vs. One-vial Taxotere (RLD)

Ingredient	Docetaxel Injection, Non-Alcohol Formula (mg/mL; % in concentrate; % in dilution)	One-Vial Taxotere (RLD) (mg/mL; % in concentrate; % in dilution)	IIG Limits (%)
Docetaxel[1]	20; [redacted]%	20; [redacted]%	
Soybean oil	27.5; [redacted]%	N/A	10%[2]
Polysorbate 80	585; [redacted]%	540; [redacted]%	50%[2]
Polyethylene glycol (PEG) 300	442.2; [redacted]%	N/A	65%[2]
Citric acid, [redacted]	10; [redacted]%	N/A	41.363%[2]
Dehydrated alcohol	N/A	395; [redacted]%	

[1] [redacted]
[2] IIG limit for iv infusion.

In comparison to the LD drug product, the TPU formulation does not contain alcohol, but contains soybean oil, PEG 300 and citric acid as new inactive ingredients. PEG 300 and citric acid have been used in approved Docetaxel Injection products. The amount of Polysorbate 80 was slightly higher than the amount used in the LD and the IIG limit. The increase in Polysorbate 80 amount was determined to be acceptable by the CMC and Pharm/Tox review teams according to the Agency's written response dated 08/19/2013 (see DARRTS document in NDA 205934 dated 08/19/2013). The amounts of the other excipients used in the formulation are below the IIG limits for parenteral use, as shown in Table 33-1 above.

Data to Support Biowaiver Request:

In the written response to TPU's Type C meeting request (dated 08/19/2013), FDA recommended that the Applicant should provide the following information as part of the biowaiver request.

- Osmolality and pH comparisons between your proposed formulation and the reference product (diluted in both 0.9% NaCl solution and 5% dextrose solution at 0.3 mg/mL and 0.74 mg/mL).
- Information that indicates whether the difference in inactive ingredients might affect the distribution or elimination of docetaxel in vivo.
- Physical [redacted] characterization comparisons between your proposed formulation and the reference product (e.g. [redacted])

In response, TPU provided the following information in the NDA.

- Osmolality and pH comparison:

The pH and osmolality of Docetaxel Injection, Non-Alcohol Formula and Taxotere (LD) were determined after dilution in 0.9% Sodium Chloride (NaCl) solution and 5% Dextrose solution to docetaxel concentrations of 0.3 mg/mL and 0.74 mg/mL. The results are summarized in Table 33-2:

Table 33-2. pH and Osmolality comparison between Docetaxel Injection (b)(4) and Taxotere

Test	Infusion Solution	Concentration	Docetaxel Injection Concentrate	Taxotere
pH	Sodium Chloride solution, 0.9%	0.3 mg/mL	(b)(4)	(b)(4)
		0.74 mg/mL		
	Dextrose solution, 5%	0.3 mg/mL		
		0.74 mg/mL		
Osmolality (mOsm)	Sodium Chloride solution, 0.9%	0.3 mg/mL		
		0.74 mg/mL		
	Dextrose solution, 5%	0.3 mg/mL		
		0.74 mg/mL		

- Effect of Inactive Ingredients on the Distribution/ Elimination of Docetaxel in vivo

Comparison of the PK profiles of Docetaxel Formulation and Taxotere were evaluated in Beagle Dogs. The results showed that Cmax, AUC, clearance, and volume of distribution are comparable between these two groups. The details of the study will be evaluated by the Pharm/Tox review team.

- (b)(4) Characterization Comparisons

Docetaxel injection (b)(4) and Texotere were evaluated for (b)(4) when diluted in 0.9% Sodium Chloride and 5% Dextose solutions to docetaxel concentrations of 0.74 mg/mL. The results shown in the Table below suggested similarity between the two drug products.

(b)(4)

Dialysis analysis was conducted to measure the release of Docetaxel from (b)(4), and the results suggested comparable release rate from the (b)(4) in the two drug products in 5% Dextrose solution and 0.9% Sodium Chloride solution (Table 33-4 and 33-5).

(b)(4)

(b)(4)

Additional Data Provided to Support Biowaiver

- Protein Binding Study

The binding of docetaxel (at 5 nominal concentration of 0.100, 1.00, 3.00, 10.0 and 100 µg/mL) to proteins in dog and human plasma was evaluated comparing Docetaxel Injection with Taxotere. The results showed that the protein binding values were similar for the two formulations. The details of the study are evaluated by the Pharm/Tox reviewer Dr. Wimolnut Manheng, and are found acceptable.

- Complement Activation Comparison Study

An in vitro evaluation of the complement activating potential of Docetaxel Injection compared to Taxotere was performed by exposing human serum to 5 dose concentrations (100, 30, 10, 3, and 1 µg/mL) of both Docetaxel Injection and Taxotere at 2 time points (30 and 90 minutes). Docetaxel Injection showed similar or less immunogenic potential.

The results of the study were evaluated by the Pharm/Tox reviewer, Dr. Wimolnut Manheng, and were found acceptable.

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

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

Reviewer's Assessment:

This 505 (b)(2) application from TPU (Teikoku Pharma USA, Inc.) relies for its approval on FDA's findings of safety and effectiveness for the Listed Drug, and requested Biowaiver.

In response to the Agency's recommendation (dated 08/19/2013), TPU provided comparative data on osmolality, pH, in vivo distribution/elimination in dogs, and (b)(4) (b)(4) between TPU's drug product and Taxotere.

- The pH of the Docetaxel injection was constantly (b)(4) than that of the LD. The difference in pH is not expected to have any impact as the product is administered intravenously (bioavailability 100%), and consequently the difference in pH will not impact the drug distribution and elimination.
- The osmolality of the Docetaxel injection was slightly (b)(4) than that of the RLD, and it was slightly (b)(4) than the normal range of the osmolality of human plasma (the normal range is 285 310 mOsm/L). However, the difference in osmolality is unlikely to affect the drug disposition either. In addition, as the osmolality is well below 400 mOsm/L, the risk of vascular complications (e.g., phlebitis) is expected to be low.

(b)(4)

- The additional studies on protein binding and complement activation did not show significant difference between TPU's product and Taxotere. The adequacy of these studies were evaluated by the Pharm/Tox reviewer ,Dr. Wimolnut Manheng, and found acceptable.

According to 21 CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data for these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident

if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same concentration of active ingredient (docetaxel), and is the same dosage form, route of administration and indication as the LD. However, the inactive ingredients of the proposed product and the reference product are different. Although, the CFR requires that the active and inactive ingredients for the test product are the same as the reference product, based on the provided data, the difference in the inactive ingredients (soybean oil, PEG-300, and citric acid) are unlikely to impact the drug's disposition; the supporting data includes comparable physical characteristics of the (b)(4) and the solubility behavior of the active ingredient in the solution for intravenous use. Based on the overall provided data and previous data knowledge, it is concluded that the disposition of TPU Docetaxel Injection 20 mg/mL after intravenous infusion will be comparable to Taxotere.

Therefore, the Applicant's request for a biowaiver for their proposed Docetaxel product is acceptable and the biowaiver is granted.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:
A waiver of the in vivo bioequivalence study requirement is granted. From a Biopharmaceutics perspective, NDA 205934 for Docetaxel Injection (20 mg/mL) is recommended for APPROVAL.

Jing Li, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:
I concur with Dr. Jing Li's assessment and approval recommendation for NDA 205934.

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

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P.7 Container Closure System - See P.1.

(b)(4)

[redacted]

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

P.8.3 Stability Data
See P.8.2

Reviewer's Assessment: Satisfactory

R REGIONAL INFORMATION

R.1 Executed Batch Record -Executed batch records were provided for batches (b)(4) (b)(4)

Reviewer's Assessment: Satisfactory

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

(1.14.1.3, proposed.pdf)

Storage temperature: The original package is stored at 20°C and 25°C (68°F and 77°F). The drug product is supplied as (b) (4) 80 mg/4 mL and 160 mg/8 mL multi-use vials.

The Docetaxel Injection (b)(4) dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature.

The drug product requires no prior dilution with a diluent and is ready to add to the infusion solution, consisting of 0.9% Sodium Chloride solution or 5% Dextrose solution to product a final concentration of 0.3 mg/mL to 0.74 mg/mL (p. 10/59). The package insert indicates that Docetaxel Injection USP dilution for intravenous infusion is prepared by injecting a single shot/single injection of Docetaxel Injection USP (20 mg docetaxel/mL) into a 250 ml infusion bag or bottle containing either infusion solution. Docetaxel Injection (b)(4) final dilution for infusion, if stored between 2 and 25°C (36°F and 77°F) is stable for 24 hours in either 0.9% Sodium Chloride solution or 5% Dextrose

solution.

After first use and following (b) (4) needle entries and product withdrawals, Docetaxel Injection (b) (4) vials are stable for up to 28 days when stored between 2 and 8°C (36 and 46°F) and protected from light.

Note to reviewer: It is noted that in-use stability chemistry studies relevant in support of pH and % assay for up to 24 hours were included. In addition acceptable data was included for a puncture study in support of the stability and integrity of the multi-use container to prevent microbial contamination. However, no studies were performed to simulate potential microbial contamination that may occur during storage of the drug product vials or during product dilution. A deficiency will be issued requesting microbiological studies for reconstitution and dilution studies for the recommended storage for up to 24 hours at 2-25^{0}C in 0.9% Sodium Chloride solution or 5% Dextrose solution.

Reviewer's Assessment: Satisfactory

The following comment (in italics) was issued in the IR dated May 11, 2015:

Comment 10: Information request dated May 11, 2015:

Microbiological studies in support of the storage time for the diluted drug product (as stated in the proposed drug product package insert) have not been provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions (i.e., 24 hours at 2- 25^{0}C after dilution in 0.9% Sodium Chloride for Injection or 5% Dextrose). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

Please include a description of the test methods and results of studies that are designed using a minimum (b)(4)

(b)(4)

(b)(4)

(b)(4) ***Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.***

The following comment was issued in an IR conveyed to the applicant on August 4, 2015.

Comments: The preliminary response and the summarized data for the requested studies for comment 9 are acknowledged. It is indicated in the response that the actual studies and the final laboratory report will be submitted in a subsequent amendment. Once submitted, the information will be reviewed by the Agency. It is noted that the actual data and study reports for these studies are required for completion of review.

Response to Agency comment 9 in the amendment submitted on July 9, 2015 and comment 10 in amendment submitted on August 4, 2015:

A preliminary response with summarized data for the requested studies was provided in the July 9, 2015 amendment. The final laboratory report for the studies performed at (b)(4) was provided in the subsequent amendment dated August 4, 2015. Information from both amendments is being reviewed here.

The package insert indicates that the drug product requires no prior dilution with a diluent and is ready to add to the infusion solution, consisting of 0.9% Sodium Chloride solution or 5% Dextrose solution to product a final concentration of 0.3 mg/mL to 0.74 mg/mL (p. 10/59). The Docetaxel Injection USP dilution for intravenous infusion is prepared by injecting a single shot/single injection of Docetaxel Injection USP (20 mg Docetaxel/mL) into a 250 ml infusion bag or bottle containing either infusion solution. Docetaxel Injection (b)(4) final dilution for infusion, if stored between 2 and 25°C (36°F and 77°F) is stable for 24 hours in either 0.9% Sodium Chloride solution or 5% Dextrose solution.

(b)(4)

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- For sterility and pyrogen (or endotoxin) release testing for the finished drug product, how was the analytical method validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Satisfactory. Please refer to the sterility assurance review summarized under Question 29 for additional information.

2.3.P.6 Reference Standards or Materials

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

Point to consider

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

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Satisfactory. Please refer to the sterility assurance review summarized under Question 29 for additional information on container/closure integrity validation studies.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

26. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is

provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

27. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended. The Product Quality Microbiology review is adequate.

Nandini Bhattacharya, Ph.D.
Branch II/DMA/OPF/CDER

Supervisor Comments and Concurrence: I concur with the Microbiology approval recommendation
Bryan S. Riley, Ph.D.
Branch Chief
CDER/OPQ/OPF/DMA/Branch II

Note: additional reviewers can be added, as appropriate

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

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b)(4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name:	Docetaxel Injection
Dosage form, route of administration	Dosage: Yes Route: Yes	Intravenous Injection
Controlled drug substance symbol (if applicable)		Not Applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Provided and edited per labeling guidance	Adequate

Conclusion: The changes/edits are made in this section and are conveyed to the applicant by the OND.

(b) "Full Prescribing Information" Section

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

3. DOSAGE FORMS AND STRENGTHS

Docetaxel Injection Concentrate is available in 20 mg/mL (as single-dose), 80 mg/4 mL and 160 mg/8 mL (as multiple-(b)(4) dose) vials. Each mL contains 20 mg docetaxel. (b)(4)

(b)(4)

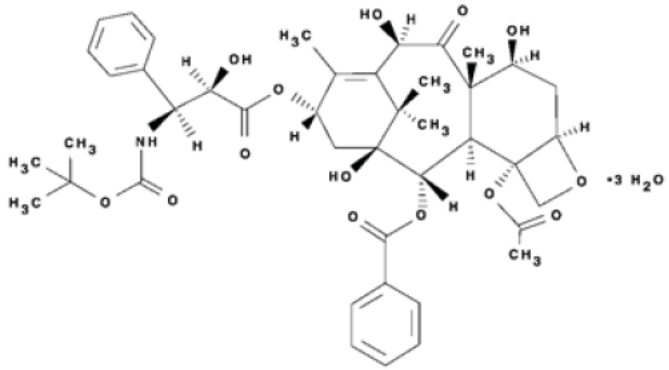
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Yes	Adequate
Strengths: in metric system	Yes	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not Applicable	Not Applicable

Conclusion: The changes/edits are made in this section and are conveyed to the applicant by the OND.

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

11. DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (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, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}•3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

Docetaxel Injection (b)(4)

Docetaxel Injection (b)(4) is a sterile, non-pyrogenic, clear, viscous, colorless to yellow solution at 20 mg/mL concentration.

Each mL contains 20 mg docetaxel (anhydrous). It also contains 27.5 mg soybean oil, 585.0 mg polysorbate 80, 10.0 mg citric acid, and 442.2 mg polyethylene glycol 300.

Docetaxel Injection (b)(4) is available in single-dose (20 mg/1 mL), and multiple-dose (b)(4) vials containing (b)(4) 80 mg (4 mL) or 160 mg (8 mL) docetaxel (anhydrous).

Docetaxel Injection (b)(4) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Docetaxel Injection	Adequate
Dosage form and route of administration	Infusion Solution	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	Yes	Adequate
Chemical name, structural formula, molecular weight	Yes	Adequate
If radioactive, statement of	N/A	Adequate

important nuclear characteristics.		
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Adequate

Conclusion: The changes/edits are made in this section and are conveyed to the applicant by the OND.

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

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Docetaxel Injection [redacted](b)(4) Non-Alcohol Formula

Docetaxel Injection [redacted](b)(4) Non-Alcohol Formula is supplied in as single-dose and multiple [redacted](b)(4) dose vials as a sterile, pyrogen-free, non-aqueous solution.

- Docetaxel Injection [redacted](b)(4) Non-Alcohol Formula 20 mg/mL single-dose [redacted](b)(4) vials in cartons containing 1 vial each (NDC XXXX-XXXX-XX)
- Docetaxel Injection [redacted](b)(4) Non-Alcohol Formula 80 mg/4 mL (20 mg/mL) multiple [redacted](b)(4) dose vials in cartons containing 1 vial each (NDC XXXX-XXXX-XX)
- Docetaxel Injection [redacted](b)(4) Non-Alcohol Formula 160 mg/8 mL (20 mg/mL) multiple [redacted](b)(4) dose vials in cartons containing 1 vial each (NDC XXXX-XXXX-XX)

16.2. Storage

Store at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from light.

After first use and following multiple needle entries and product withdrawals, Docetaxel Injection Concentrate multi-use vials are stable for up to 28 days when stored between 2°C and 8°C (36°F and 46°F) and protected from light.

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

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Yes	Adequate

Conclusion: The changes/edits are made in this section and are conveyed to the applicant by the OND.

2. Labels

(**Note:** This review captures the flavor of **one strength** of bottle label and one carton label. Other strength and carton labels will follow the same advice)

1) Immediate Container Label

(b)(4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Docetaxel Injection	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Adequate
Net contents (21 CFR 201.51(a))	Provided	Adequate
Lot number per 21 CFR 201.18	Provided	Adequate
Expiration date per 21 CFR 201.17	Provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not provided	Applicant will provide NDC #s at the end of October 2015. Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
Others	Retail in original package to Protect from light	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: The deficiencies are identified, discussed with the DMEPA and communicated. The applicant accepts the proposal via amendment dated 19-AUG-2015 and revised the labels as advised. **Adequate**

Note: *The statement on* ***PI*** *has been modified from* (b) (4) *to "****For intravenous use****" per internal draft Guidance (Product Title and Initial US Approval in the Highlights of PI for Human ……Content and Format, May 2015).*

The statement "For Intravenous Infusion Only" on container labels remains intact and informs end users to use this product for infusion and prepare an IV bag. Additionally, "For Intravenous Infusion Only" is already on the container closure labels for many existing Docetaxel injection products and helps to prevent wrong technique in administration errors (i.e. IV push).

2) Cartons

(b)(4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Docetaxel Injection	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Adequate
Net contents (21 CFR 201.51(a))	Provided	Adequate
Lot number per 21 CFR 201.18	Provided	Adequate
Expiration date per 21 CFR 201.17	Provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Provided	Adequate
Sterility Information (if applicable)	Provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not Provided	Applicant will provide NDC#s at the end of October 2015. Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Retail in original package to Protect from light Cytotoxic Agent	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Provided (IV infusion only)	Adequate

Conclusion: *The deficiencies are identified, discussed with the DMEPA and communicated. The applicant accepts the proposal via amendment dated 19-AUG-2015 and revised the labels as advised.*

As of the date of this review, the applicant states that they will require three more weeks to amend the Container/closure labels and PI with the NDC# and requests additional time that would still fall before the PDUFA date. Per 21 CFR 201.2 , the NDC number is requested but not required on all drug labels and in all drug labeling, including the label of any prescription drug furnished to a consumer. Therefore, since labeling negotiations are on-going and labeling will not be finalized until closer to the PDUFA date of December 2015, it is reasonable to grant the applicant's request to provide the NDC #s within their suggested timeframe.

Revisions to the proposed PI labeling (Highlight, Description and How Supplied sections) have been conveyed to the OND PM and will be finalized during team review of the labeling. The NDC # can be added when it becomes available. ***Adequate***

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	Refer to Product Quality Microbiology review	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin (b) (4)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Refer to Product Quality Microbiology Review	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose	• Formulation • Container closure				Controls are in place, fill volume is kept the same

(Fill Volume/deliverable volume)	• Process parameters • Scale/equipments • Site	L	Controlled via specs	Acceptable	as that of the LD (see pharmaceutical development report)
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development	Acceptable	Monitor post marketing safety report for unusual application site reaction in conjunction with the clinician
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	**Controlled via specs during stability**	Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled via specs	Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • **Container closure** • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development	Acceptable	Controlled via DMF
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs	Acceptable	Controls are in place

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 205934	**Submission Type: Standard Review**	**Established/Proper Name: Docetaxel Injection**
Applicant: Teikoku Pharma USA, Inc.	**Letter Date: February 26, 2014**	**Dosage Form: Injection, Solution, (b)(4)**
Chemical Type: Type 3	**Stamp Date: February 26, 2014**	**Strength: 20 mg/mL, 80 mg/4 mL, 160 mg/8 mL**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Describe potential review issues here or on additional sheets

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☒	☐	
4.	Narrow Therapeutic Index Drug	☒	☐	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
	Regulatory Considerations				
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other		☐	☐	
	Quality Considerations				
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☒	☐	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other		☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance	☒	☐	☐	No information was submitted for the section of "Adventitious Agents Safety Evaluation". No information was submitted for the

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols				section of "Method Validation Package" or "Comparability Protocols".
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☐	☐	☒	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	There are no in vivo BA or BE studies submitted. The Applicant requested biowaiver for this injectable drug product.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	N/A
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	designation claim as per the CFR?				
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☐	☒	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 205934	**Submission Type: Standard Review**	**Established/Proper Name: Docetaxel Injection**
Applicant: Teikoku Pharma USA, Inc.	**Letter Date: February 26, 2014**	**Dosage Form: Injection, Solution, (b)(4)**
Chemical Type: Type 3	**Stamp Date: February 26, 2014**	**Strength: 20 mg/mL, 80 mg/4 mL, 160 mg/8 mL**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Describe potential review issues here or on additional sheets

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☒	☐	
4.	Narrow Therapeutic Index Drug	☒	☐	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
	Regulatory Considerations				
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other		☐	☐	
	Quality Considerations				
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
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34.	Process Analytical Technology[1]		☐	☒	
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37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
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41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☒	☐	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
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	designation claim as per the CFR?				
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