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RESEARCH**

APPLICATION NUMBER:

202356Orig1s000

PHARMACOLOGY REVIEW(S)

**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: 202356
Supporting document: 19 (eCTD Sequence Number 18)
Applicant's letter date: September 12, 2013
CDER stamp date: September 13, 2013
Product: Docetaxel Injection
Indication: Breast cancer, non-small cell lung cancer,
prostate cancer, gastric adenocarcinoma, and
head and neck cancer.
Applicant: Pfizer Labs
235 East 42nd Street
New York, NY 10017
Review Division: Division of Hematology Oncology Toxicology
(DHOT) for Division of Oncology Products 1
(DOP1)
Reviewer: Haw-Jyh Chiu, Ph.D.
Supervisor/Team Leader: Todd R. Palmby, Ph.D.
Division Director: John K. Leighton, Ph.D., D.A.B.T. (Acting,
DHOT)
Anthony Murgio, M.D. (DOP1)
Project Manager: Modupe O. Fagbami

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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 202356.

MEMORANDUM

TO: The file
CC: Todd R. Palmby, Ph.D., Supervisory Toxicologist, Division of Hematology Oncology Toxicology (DHOT), Office of Hematology and Oncology Products (OHOP), Center for Drug Evaluation and Research (CDER)
FROM: Haw-Jyh, Ph.D, Toxicologist, DHOT, OHOP, CDER

NDA #: 202356
SDN: 19
SPONSOR: Pfizer Labs
PRODUCT: Docetaxel Injection

SUBMISSION TYPE: 505(b)(2) NDA application; Class 2 resubmission

DATE: February 24, 2014

EXECUTIVE SUMMARY

On September 12, 2013, Pfizer submitted this NDA 202356 Class 2 Resubmission for Docetaxel Injection. In this resubmission, Pfizer provided information to address product quality and clinical deficiencies identified during the review of the last NDA resubmission and outlined in the Complete Response Letter send to the Sponsor by FDA on February 14, 2013. There were no nonclinical issues identified in the Complete Response Letter and Pfizer did not submit any new nonclinical data in this resubmission.

Recommendations**Approvability**

The nonclinical discipline recommended NDA 202356 for Docetaxel Injection for approval following review of nonclinical data provided in the previous resubmission. From the nonclinical perspective, since no new nonclinical data were provided and the overall nonclinical information in NDA 202356 has not changed, this resubmission of NDA 202356 for Docetaxel Injection is recommended for approval for the proposed indications.

Additional Non Clinical Recommendations

None.

Labeling

No labeling changes are recommended from the perspective of the nonclinical discipline.

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/s/

HAW-JYH CHIU
02/24/2014

TODD R PALMBY
02/24/2014

**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: 202356
Supporting document: 12
Applicant's letter date: August 14, 2012
CDER stamp date: August 14, 2012
Product: Pfizer Docetaxel Injection Concentrate
10 mg/mL
Indication: Breast cancer, non-small cell lung cancer,
prostate cancer, gastric adenocarcinoma, and
head and neck cancer.
Applicant: Pfizer Labs
235 East 42nd Street
New York, NY 10017
Review Division: Division of Hematology Oncology Toxicology
(DHOT) for Division of Oncology Products 1
(DOP1)
Reviewer: Haw-Jyh Chiu, Ph.D.
Team Leader: Todd R. Palmby, Ph.D.
Division Director: John K. Leighton, Ph.D., D.A.B.T. (DHOT)
Robert L. Justice, M.D. (DOP1)
Project Manager: Christy Cottrell

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MEMORANDUM

TO: The file
CC: Todd R. Palmby, Ph.D., Supervisory Pharmacologist, Division of Hematology Oncology Toxicology (DHOT), Office of Hematology and Oncology Products (OHOP), Center for Drug Evaluation and Research (CDER)
FROM: Haw-Jyh, Ph.D, Toxicologist, DHOT, OHOP, CDER

NDA #: 202356
SDN: 12
SPONSOR: Pfizer Labs
PRODUCT: Pfizer Docetaxel Injection Concentrate 10 mg/mL
SUBMISSION TYPE: 505(b)(2) NDA application; Class 2 resubmission

DATE: January 14, 2013

EXECUTIVE SUMMARY

On August 14, 2012, Pfizer submitted this NDA 202356 Resubmission for Docetaxel Injection Concentrate. In this resubmission, Pfizer addressed two nonclinical-related deficiencies contained in the Completed Response Letter for the original NDA submission. These comments were in regards to impurity specification and leachable levels for Docetaxel Injection Concentrate. In response to the Complete Response Letter, the Applicant revised the impurity specification for Docetaxel Injection Concentrate to levels either not exceeding those detected in the reference listed drug, Taxotere, or below those indicated in the USP monographs for docetaxel drug substance or docetaxel injection drug product. The levels of leachables have also been characterized and the Applicant has set the acceptance levels based on the levels of leachables detected during stability testing of Docetaxel Injection Concentrate. The Applicant also provided literature-based risk assessments to justify the levels of these leachables in Docetaxel Injection Concentrate. Overall, from the perspective of the nonclinical discipline, the proposed impurity specification and justification for the levels of leachables in Docetaxel Injection Concentrate are acceptable for the proposed indications.

Recommendations**Approvability**

Based on the non-clinical information submitted with NDA 202356, Docetaxel Injection Concentrate is recommended for approval for the proposed indications from the perspective of the nonclinical discipline.

The Applicant adequately responded to nonclinical deficiencies regarding impurities and leachables contained in the previous Complete Response Letter. However, the justification of the levels of two excipients, ethanol and propylene glycol, was not adequate for the review team to conclude within a reasonable level of uncertainty that

there will not be an associated change in the risk to benefit ratio compared to the listed drug. Conducting additional nonclinical studies is not warranted to resolve this deficiency, which is why from a nonclinical perspective this application was deemed approvable.

Additional Non Clinical Recommendations

None.

Labeling

No labeling changes are recommended from the perspective of the nonclinical discipline.

This review is focused on the new nonclinical information provided in support of this Class 2 NDA Resubmission. Specifically, the Applicant provided information to support the proposed impurity specification and safety of leachables in the drug product. In addition, this review will also briefly summarize information provided by the Applicant in support of the levels of ethanol and propylene glycol in Docetaxel Injection Concentrate. Please refer to the Pharmacology/Toxicology NDA Review and Evaluation of the original NDA 202356 submission in DARRTS for a full review of NDA 202356.

Impurities

Nonclinical Deficiency 1 from Complete Response Letter

You have not provided adequate scientific justification for the proposed levels of impurities. The proposed acceptance criteria for all identified impurities in the Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance, or to not exceed the levels detected in Taxotere. If you cannot lower the specifications as advised, you must conduct nonclinical studies to qualify these impurities, or provide sufficient data from the literature to adequately justify these proposed impurity levels.

Applicant's Response

Pfizer revised the impurity specification for Docetaxel Injection Concentrate to either below levels detected in the Taxotere or to levels below those indicated in the USP monographs for docetaxel drug substance or docetaxel injection drug product, as shown below:

Nomenclature	Pfizer specifications for Docetaxel Injection	USP specifications for Docetaxel Injection	Comments
(b) (4) 2-Debenzoxyyl 2-pentenoyl docetaxel	nmt (b) (4) %	(none)	Pfizer specifications complies with USP specification for Docetaxel drug substance (nmt (b) (4) %)
(b) (4) 6-Oxodocetaxel	nmt (b) (4) %	nmt 1.5%	Complies with USP
(b) (4) 4-Epidocetaxel	nmt (b) (4) %	nmt (b) (4) % ¹	Complies with USP
(b) (4) 4-Epi-6-oxodocetaxel	nmt (b) (4) %	nmt 0.5%	Complies with USP
(b) (4)	nmt (b) (4) %	(none)	Pfizer specifications does not exceed levels detected in Taxotere (b) (4) % at the 24-month test interval)
Other individual impurity	nmt (b) (4) %	nmt 0.2%	Complies with USP
Total impurities	nmt (b) (4) %	nmt 3.5%	Complies with USP

nmt = not more than

1 = Since the release of the finalized monograph in February 2012 for USP35, the USP posted a Revision Bulletin in April 2012, to further widen the limits of Impurity (b) (4) "nmt 1.0%", in order to reflect FDA-approved specifications. The Revision Bulletin will be incorporated into USP36. Pfizer's limits of "nmt (b) (4) %" for Impurity (b) (4) continue to comply with the USP monograph for Docetaxel Injection, in USP35 and USP36.

[Excerpted from Applicant's submission]

Reviewer's Assessment

The proposed impurity specifications are acceptable from the nonclinical perspective.

Leachables

Nonclinical Deficiency 2 from Complete Response Letter

You have not provided complete information regarding the levels and the safety of the leachables present in your drug product, in order for FDA to adequately evaluate their safety at the acceptance levels and expiry date proposed in your submission of December 1, 2011. Please provide this information as well as information regarding the safety of each of these leachables after intravenous administration. If you cannot qualify the safety of the levels of each of the detectable leachables from data in the literature, additional nonclinical studies will be needed.

Applicant's Response

In response to an Information Request by FDA, Pfizer provided an amendment to this NDA (SDN-7, dated December 1, 2011) which includes preliminary results from an evaluation of the drug product for compounds that may leach from elastomeric or plastic components of the container closure system. Pfizer stated that the following leachables have been detected in the drug product: (b) (4)

[Redacted] (b) (4)

Pfizer did not qualify these leachables by conducting any nonclinical animal toxicity studies, but instead provided a literature-based assessment of the safety of the estimated total daily intake of these leachables. The following table lists the identified leachables, levels detected in stability samples, estimated Total Daily Intake (TDI), and the Applicant's proposed allowable TDI levels.

Identified Leachables	Maximum Levels Detected on Stability (µg/ml)	Proposed Analytical Acceptance Criteria (µg/mL)	Proposed Total Daily Intake (µg)
(b) (4)			

In calculating the safety margins for leachables detected in Docetaxel Injection Concentrate, Pfizer used the following uncertainty factors where appropriate:

Modification	Uncertainty Factor (UF)
oral administration (animal) to intravenous (human)	10
variability relative to human sensitivity	10
extrapolation from mouse to human	12
extrapolation from rat to human	5
extrapolation from dog to human	2

[Excerpted from Applicant's submission]

level for dietary intake, and 2-fold lower than the amount of (b) (4) present in marketed (b) (4).

(b) (4)
Based on the acceptance criteria of (b) (4) $\mu\text{g/mL}$ (b) (4), Pfizer proposed a total daily intake of (b) (4) μg (b) (4) in Docetaxel Injection Concentrate. Pfizer provided a risk assessment for the proposed level of (b) (4) in the drug product based on data from clinical studies following administration of (b) (4)-containing (b) (4). Specifically, following oral administration of (b) (4) to humans, median plasma concentrations of (b) (4) have been found to range from (b) (4) to (b) (4).^{4,5} The theoretical maximum plasma level of (b) (4) following administration of Docetaxel Injection Concentrate is (b) (4) ng/mL (b) (4), which is below plasma levels of (b) (4) found following (b) (4) administration. In addition, (b) (4)

Administration of (b) (4) μg of (b) (4) in Docetaxel Injection Concentrate to a 60 kg patient would result in a dose of (b) (4) $\mu\text{g/kg/day}$, which is 4 to 5 times less than the levels associated with toxicity in the (b) (4).

(b) (4)
Based on the acceptance criteria of (b) (4) $\mu\text{g/mL}$ (b) (4), Pfizer proposed a total daily intake of (b) (4) μg (b) (4) in Docetaxel Injection Concentrate. (b) (4) is classified (b) (4)

(b) (4)
Based on the acceptance criteria of (b) (4) $\mu\text{g/mL}$ (b) (4), Pfizer proposed a total daily intake of (b) (4) μg iron in Docetaxel Injection Concentrate. (b) (4) is classified (b) (4)

4 (b) (4)
5 (b) (4)
6 (b) (4)
(b) (4)
(b) (4)

(b) (4)
(b) (4)
9

(b) (4)
(b) (4)

Pfizer proposed a total daily intake of (b) (4) μg (b) (4) and (b) (4) μg (b) (4) plus (b) (4) (b) (4) in Docetaxel Injection Concentrate.

For (b) (4), based on the NOEL of (b) (4) $\text{mg}/\text{kg}/\text{day}$ (b) (4),

Pfizer estimated a relatively safe TDI to be (b) (4) $\mu\text{g}/\text{kg}/\text{day}$, or 115 times the proposed TDI. Although Pfizer did not provide data bridging the toxicity profiles among (b) (4) and (b) (4), these compounds appear to have similar lethal doses, as shown below:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

(b) (4)
Based on the acceptance criteria of (b) (4) $\mu\text{g}/\text{mL}$ (b) (4), Pfizer proposed a total daily intake of (b) (4) μg (b) (4) in Docetaxel Injection Concentrate. Although toxicity information for (b) (4) based on intravenous administration is limited,

8 (b) (4)
(b) (4)
(b) (4)
(b) (4)
11 (b) (4)
(b) (4)

Pfizer provided the following data^{17,18,19} regarding the blood alcohol levels following intravenous infusion with ethanol:

Study Author	Infusion Rate	Approximate total daily intake	Duration of infusion	Blood alcohol level at the end of infusion
Jones et al ¹	0.4 g ethanol per kg body weight	28 g ethanol for a 70 kg individual	0.5h	84.7 mg/dL*
Jones et al ²	0.6 g ethanol per kg body weight	42 g ethanol for a 70 kg individual	1h	108 mg/dL*
Rangno et al ³	0.375 g ethanol per kg body weight	26.3 g ethanol for a 70kg individual	0.5h	88 mg/dL [†]

* Venous blood alcohol level reported
† Plasma alcohol level reported

[Excerpted from Applicant's submission]

The Handbook of Pharmaceutical Excipients (2009) lists the LD₅₀ of intravenous infusion of ethanol to be 1.97 g/kg and 1.44 g/kg, in mice and rats, respectively.

Pfizer stated that blood alcohol levels exceeding 100 mg/dL can result in impairment of motor function, including ataxia and lack of co-ordination, while blood alcohol levels less than 50 mg/dL can result in increased talkativeness, increased relaxation, and impairment of performing certain tasks.²⁰ Pfizer further states that based on the maximum level of 6.4 g ethanol infused with Docetaxel Injection Concentrate and available data on intravenous infusion of ethanol, the blood alcohol level following administration of Docetaxel Injection Concentrate should be significantly lower than 50 mg/dL.

The European guidance document, Volume 3B (July 2003), Excipients in the label and package leaflet of medicinal products for human use, recommends that drug product which contain a propylene glycol TDI of 400 mg/kg should include a "may cause alcohol-like syndrome" safety statement. In general, high levels of propylene glycol may contribute to alcohol-like syndrome. The Handbook of Pharmaceutical Excipients (2009) lists the LD₅₀ of intravenous infusion of propylene glycol to be 6.63 g/kg and 6.42 g/kg, in mice and rats, respectively.

Reviewer's Assessment

Based on discussions with the review team for NDA 202356, the proposed justifications for levels of ethanol and propylene glycol in Docetaxel Injection Concentration for this 505(b)(2) application are not sufficient to determine that there is not an increased safety risk compared to the listed drug, Taxotere. An example of experience with the proposed total daily intake of ethanol and propylene glycol in the same drug product was not provided by the Applicant. From the nonclinical perspective, conducting new nonclinical toxicology studies with ethanol and propylene glycol to qualify their

¹⁷ Jones AW *et al. J Forensic Sci.* (1997); 42: 1008-1094.

¹⁸ Jones AW *et al. Eur J Clin Pharmacol* (1992) ; 42 : 445-448.

¹⁹ Rangno RE, *et al. Br J Clin Pharmacol* (1981) ; 12 : 667-673.

²⁰ Vonghia L, *et al. Eur J Intern Med* (2008); 19: 561-567.

respective levels in Docetaxel Injection Concentrate is not warranted given the breadth of clinical experience regarding effects of alcohol correlating with blood alcohol levels. Additional data from nonclinical studies with Docetaxel Injection Concentration will likely not be useful in changing the risk assessment of the proposed levels of ethanol and propylene glycol. Refer to the clinical review of this NDA for more detailed information about the remaining uncertainty surrounding the potential risks associated with the proposed ethanol and propylene glycol levels from a clinical perspective.

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/s/

HAW-JYH CHIU
01/15/2013

TODD R PALMBY
01/15/2013

**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: 202356
Supporting document: 7
Applicant's letter date: December 1, 2011
CDER stamp date: December 1, 2011
Product: Pfizer Docetaxel Injection Concentrate
10 mg/mL
Indication: Breast cancer, non-small cell lung cancer,
prostate cancer, gastric adenocarcinoma, and
head and neck cancer.
Applicant: Pfizer Labs
235 East 42nd Street
New York, NY 10017
Review Division: Division of Hematology, Oncology, Toxicology
(DHOT) for Division of Oncology Products 2
(DOP2)
Reviewer: Haw-Jyh Chiu, Ph.D.
Supervisor/Team Leader: Anne M. Pilaro, Ph.D.
Division Director: John K. Leighton, Ph.D., D.A.B.T. (DHOT)
Patricia Keegan, M.D. (DOP2)
Project Manager: Sharon Sickafuse

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MEMORANDUM

TO: The file
CC: Anne M. Pilaro, Ph.D., Supervisory Toxicologist, Division of Hematology, Oncology, Toxicology (DHOT), Office of Hematology and Oncology Products (OHOP), Center for Drug Evaluation and Research (CDER)
FROM: Haw-Jyh, Ph.D, Toxicologist, DHOT, OHOP, CDER

NDA #: 202356
SDN: 7
SPONSOR: Pfizer Labs
PRODUCT: Pfizer Docetaxel Injection Concentrate 10 mg/mL

SUBMISSION TYPE: Original 505(b)(2) NDA application; **addendum to initial primary review document**

DATE: February 14, 2012

Executive Summary

In response to an Information Request by FDA, Pfizer provided an amendment to this NDA (SDN-7, dated December 1, 2011) which includes preliminary results from an evaluation of the drug product for compounds that may leach from elastomeric or plastic components of the container closure system. Pfizer stated that the following leachables have been detected in the drug product: (b) (4)

[Redacted]

Pfizer did not qualify these leachables with any nonclinical animal toxicity studies, but instead provided a literature-based assessment of the safety of the estimated total daily intake of these leachables. The following table lists the identified leachables, levels detected in stability samples, estimated Total Daily Intake (TDI), and the Sponsor's proposed allowable TDI levels.

Identified Leachables	Levels detected on stability	Estimated TDI	Proposed TDI*
[Redacted]			

* These values proposed by the Sponsor were adjusted from the “Estimated Total Daily Intake” based on analytical variability for these trace analyses.
[From information provided in the amendment]

However, based on the review of this amendment by the CMC reviewer, Dr. Josephine Jee, Pfizer did not provide sufficient data for FDA to adequately review the safety these leachables. Specifically, Dr. Jee stated that Pfizer has not provided raw data, or a description of the complete analytical procedures or methodologies used to detect these leachables. Also, Dr. Jee could not determine how and when these leachables were measured, and the basis for their proposed TDI values.

From the nonclinical perspective, in the absence of these data, the nonclinical discipline cannot make at this time a full determination of the safety of either these leachables themselves, or the amount of each of these leachables that would be present in the drug product at the proposed specifications at the proposed 24-month expiry.

Furthermore, based on the review of the information contained in this amendment and a literature-based assessment of these identified leachables, this reviewer found that the Applicant has not provided adequate information to describe the safety of these leachables when administered to patients intravenously with the drug product.

Recommendations

From the nonclinical perspective, based on insufficient CMC information provided in this NDA amendment, the Applicant has provided inadequate justification for the proposed levels of leachables in Pfizer Docetaxel Injection Concentrate.

Non Clinical Recommendations to Applicant

You have not provided complete information regarding the levels, nor safety of the leachables present in your drug product in order for FDA to adequately evaluate their safety at the acceptance levels and expiry date proposed in this NDA amendment. Provide this information to the NDA. Additionally, provide information to the NDA regarding the safety of each of these leachables after intravenous administration. If you cannot qualify the safety of the levels of each of the detectable leachables from data in the literature, additional nonclinical studies will be needed to qualify their safety.

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/s/

HAW-JYH CHIU
02/14/2012

ANNE M PILARO
02/14/2012

I concur with the reviewer's conclusions and identification of the lack of information regarding the safety of the leachables from the container-closure system, and the recommendation that this deficiency be communicated to the sponsor as part of the Complete Response letter for this NDA.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202356
Supporting document: 1
Applicant's letter date: April 29, 2011
CDER stamp date: April 29, 2011
Product: Pfizer Docetaxel Injection Concentrate
10 mg/mL
Indication: Breast cancer, non-small cell lung cancer,
prostate cancer, gastric adenocarcinoma, and
head and neck cancer.
Applicant: Pfizer Labs
235 East 42nd Street
New York, NY 10017
Review Division: Division of Hematology, Oncology, Toxicology
(DHOT) for Division of Oncology Products 2
(DOP2)
Reviewer: Haw-Jyh Chiu, Ph.D.
Supervisor/Team Leader: Anne M. Pilaro, Ph.D.
Division Director: John K. Leighton, Ph.D., D.A.B.T. (DHOT)
Patricia Keegan, M.D. (DOP2)
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1 Executive Summary

1.1 Introduction

Pfizer submitted this New Drug Application (NDA) for Docetaxel Injection Concentrate, 10 mg/mL, as a 505(b)(2) application, for the same clinical indications (breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer), route of administration, dosages, and dosing schedule as Taxotere[®], the reference listed drug (RLD). Pfizer Docetaxel Injection Concentrate 10 mg/mL differs from Taxotere[®] with respect to the hydrate form of the active ingredient, excipient composition, and container system. Pfizer Docetaxel Injection Concentrate 10 mg/mL is a 1-vial formulation of docetaxel (anhydrous) which will be supplied in polypropylene vials. Taxotere is supplied as a 2-component “pre-mix” system of docetaxel (trihydrate) and is supplied in glass vials.

1.2 Brief Discussion of Nonclinical Findings

Pfizer did not conduct any new GLP-compliant, toxicology studies with docetaxel in support of this NDA. In the submission, a literature reference¹ was included to provide a summary of pharmacology, pharmacokinetic, and toxicology studies conducted by Sanofi in support of the original application for the RLD, Taxotere. Four non-GLP studies were conducted to compare the pharmacokinetic in dogs, protein binding and micelle release, local tolerance, and blood compatibility between Pfizer Docetaxel Injection Concentrate 10 mg/mL and Taxotere[®].

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, the applicant has provided inadequate scientific justification for the levels of impurities proposed in this NDA submission, and the proposed specifications should be revised before this NDA can be recommended for approval.

1.3.2 Non Clinical Recommendations to Applicant

You have provided inadequate scientific justification for the levels of impurities proposed in this NDA submission. The proposed acceptance criteria for all identified impurities in the Pfizer Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance or not to exceed the levels detected in Taxotere[®]. Alternatively, either conduct nonclinical studies to qualify these impurities, or provide data from the literature to adequately justify these proposed impurity levels.

1.3.3 Labeling

The content of the pharmacology/toxicology sections of the label is the same as that of the referenced listed drug, Taxotere®.

2 Drug Information

2.1 Drug

CAS Registry Number: 114977-28-5 (docetaxel, anhydrous)

Generic Name: Pfizer Docetaxel Injection Concentrate 10 mg/mL

Code Name: Not available.

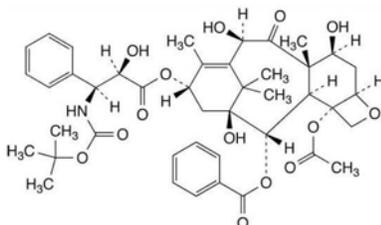
Chemical Name:



Molecular Formula: $C_{43}H_{53}NO_{14}$

Molecular Weight: 807. (b) (4) Daltons

Structure:



Pharmacologic Class: Microtubule inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 20449 (Reference Listed Drug)

2.3 Drug Formulation

The drug product is a clear, colorless to brown-yellow solution, packaged in 2 mL, (b) (4) mL, and 20 mL polypropylene vials.

Table 1. Composition of the formulation for Taxotere and Pfizer Docetaxel Injection Concentrate drug product.

Name and Function of Ingredient	Taxotere	Pfizer Docetaxel Injection Concentrate
Docetaxel (anhydrous) – active ingredient	10 mg/mL	10 mg/mL
Polysorbate-80 - (b) (4)	(b) (4) % v/v	(b) (4) % v/v
Propylene glycol - (b) (4)	-	(b) (4) % v/v
Disodium edentate – (b) (4)	-	0.01 mg/mL
Ethanol - (b) (4)	(b) (4) % v/v	40% v/v
Anhydrous citric acid – pH adjustment	-	(b) (4) (b) (4) 3.5 mg/mL)
Water for Injection - Diluent	(b) (4) % v/v	(b) (4)

2.4 Comments on Novel Excipients

All excipients are listed in the FDA Inactive Ingredient Database, and are present in other drug products approved by FDA for intravenous infusion.

2.5 Comments on Impurities/Degradants of Concern

Studies conducted by Pfizer showed that Pfizer Docetaxel Injection Concentrate (b) (4) impurities when compared to Taxotere®. (b) (4)

Docetaxel Injection Concentrate and Taxotere® over the proposed two-year shelf-life period.

Table 2. Impurity Specification for Pfizer Docetaxel Injection Concentrate.

Impurities	Acceptance criteria (b) (4)
(b) (4)	

Table 3. Summary of stability data for Taxotere and Pfizer Docetaxel Injection Concentrate.

Test Parameters	Pfizer Docetaxel Injection 10mg/mL			Taxotere		
	Range (initial)	Range (stability)	Estimated increase over two years ¹	Range (initial) ²	Range (stability)	Estimated increase over two years ¹
(b) (4)						(b) (4)
Other ind. imp.						
Total impurities						

¹ Calculated based on regression analysis of long term results up to the 12-month test interval, at 25°C/60% relative humidity. See Section 3.2.P.8.1 Stability Summary and Conclusion.

² Taxotere batch D8A664 was manufactured in Jun-08. Batch D8A664 was placed on Pfizer's stability program and tested in Feb-09. All subsequent references to testing intervals and timepoints for Batch D8A664 relate to the initial testing by Pfizer in Feb-09. See Section 3.2.P.8.1 Stability Summary and Conclusion, and Section 3.2.P.8.3 Stability Data.

[Adapted from Table 3.2.P.5.6-5, on page 4 in Section 3.2.P.5.6 of the original NDA submission.]

The proposed drug product specification was not found to be acceptable by the CMC review team, who have requested Pfizer to revise the specification. The following impurity specification-related CMC Information Request was sent to Pfizer on October 7, 2011:

“Revise the drug product specification to include a single set of criteria for product release and for use in stability studies. Base this specification on the results of batch analyses, manufacturing capability, and stability data.”

Reviewer’s comments:

- Specifications listed in Table 2 represent revised specifications provided to FDA on December 1, 2011, in response to an Information Request by FDA. However, the new proposed specifications are still above levels consistent with those specified in the ICH Q3B Guidance, and above the levels detected in Taxotere[®]. From the nonclinical perspective, any levels above those in Taxotere should be adequately justified based on data from nonclinical or clinical studies.
- In the same NDA amendment dated December 1, 2011, Pfizer provided some information regarding preliminary studies on leachable compounds in the drug product. However, at the time this review was completed, the CMC reviewer stated that no supporting data was provided to allow FDA to adequately review the safety of the levels of these leachables; therefore, the nonclinical discipline will not review this preliminary information at the present time.

2.6 Proposed Clinical Population and Dosing Regimen

Same as Taxotere[®].

2.7 Regulatory Background

A pre-IND/pre-NDA meeting was held under IND 109463 on November 1, 2010 between FDA and representative from Pfizer to discuss the Sponsor's plan to submit a 505(b)(2) application for Pfizer Docetaxel Injection Concentrate, 10 mg/mL.

3 Studies Submitted

3.1 Studies Reviewed

Study Number	Study title	Study Report eCTD Location
0432-2010	Docetaxel Pfizer Injection and Taxotere [®] : Evaluation of pharmacokinetics following single IV (infusion) administration to Beagle dog.	4.2.2.2.
0433-2010	Plasma protein binding and micelle release determination using docetaxel Pfizer Injection and Taxotere [®] .	4.2.2.3.
10LJ041	Local vascular tissue irritation study of docetaxel and Taxotere in female rabbits.	4.2.3.6.
09LJ059	Docetaxel [0.9 mg/mL] in 0.9% NaCl, docetaxel [0.9 mg/mL] in 5% glucose, and Sanofi Taxotere [0.9 mg/mL] in 0.9% NaCl: Report for the in vitro compatibility of the parenteral formulation with human blood.	4.2.3.7.7.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

Pfizer did not conduct any pharmacology studies in support of this NDA submission.

5 Pharmacokinetics/ADME/Toxicokinetics

Pfizer conducted a pharmacokinetic study (Study No. 0432-2010) and an *in vitro* plasma binding and micelle release study (Study No. 0433-2010) to compare Pfizer Docetaxel Injection concentrate to Taxotere[®]. The results from these studies are briefly summarized below:

- **Study No. 0432-2010: “Docetaxel Pfizer Injection and Taxotere[®]: Evaluation of pharmacokinetics following single IV (infusion) administration to Beagle dog.”**
 - Study design
 - Ten male dogs were assigned to two groups (5 animals/group) and on Days 1 and 23 were administered 1 mg/kg docetaxel (Pfizer Docetaxel Injection Concentrate or Taxotere[®]) as a 20-minute IV infusion, following a cross-over design.
 - Blood samples were collected at pre-dose, 10 min and 20 min (end of infusion) and then 5, 10, 20, 30 min, 1, 2, 4, 8, 12, 24, 36, and 48 hours after the end of infusion.
 - Docetaxel was assayed using an LC-MS-MS methods.
 - Results
 - There were no mortalities in the study.
 - There were no significant differences in incidence of clinical signs.
 - Similar plasma profiles of docetaxel were noted following administration of either Pfizer Docetaxel Injection Concentrate or Taxotere[®].
 - A summary of PK parameters is shown below:

Table 4. Descriptive statistics of PK parameters in male dogs after 20 minute infusion of 1 mg/kg docetaxel Pfizer Injection and Taxotere.

Descriptive Statistics	Docetaxel Pfizer Injection		Taxotere [®]	
	C _{max}	AUC _{0-t(last)}	C _{max}	AUC _{0-t(last)}
	(ng/mL)	(ng·h/mL)	(ng/mL)	(ng·h/mL)
Geometric mean	1420	507	1590	576
Arithmetic mean	1460	518	1590	582
SD	378	117	151	87.4
n	10	10	10	10

[Copied from Table 10.1, on page 12 of Study Report No. 0432-2010-nonclinical-data]

Analysis	Parameter	Docetaxel/Taxotere [®]	90% Confidence Interval	
			Lower	Upper
Unadjusted for Dose	AUClast	0.880	0.802	0.965
	C _{max}	0.895	0.803	0.997
Adjusted for Dose	AUClast	0.949	0.866	1.041
	C _{max}	0.966	0.867	1.077

[Copied from table on page 1 of Study Report No. 0432-2010-statistical]

- Conclusions
 - There were no statistically significant differences in exposure parameters (C_{max} and AUC_{0-t(last)}) between Pfizer Docetaxel Injection Concentrate and Taxotere[®].

Reviewer’s comments:

Raw data from this study were independently analyzed by the clinical pharmacology reviewer assigned to this application (Dr. Lilian Hua Zhang), who verified that the PK parameters fell within the 90% confidence interval.

- **Study No. 0433-2010: “Plasma protein binding and micelle release determination using docetaxel Pfizer Injection and Taxotere®.”**
 - Study design
 - Plasma protein binding of docetaxel Pfizer Docetaxel Injection Concentrate was compared to that of Taxotere® using *in vitro* equilibrium analysis of *ex vivo* plasma samples from dogs and humans, including selected plasma samples from dogs used in Study No. 0432-2010.
 - *In vitro* release of docetaxel from micelles from Pfizer Docetaxel Injection Concentrate in infusion solution was compared to that of Taxotere®.
 - Docetaxel was assayed using an LC-MS-MS method.
 - Results
 - The plasma protein binding of docetaxel was comparable (95-97%) in dog and human plasma samples incubated with Pfizer Docetaxel Injection Concentrate or Taxotere®.
 - *In vitro* release of docetaxel from micelles was slow, and similar between Pfizer Docetaxel Injection Concentrate and Taxotere®. After 24 hours of dialysis, the percentage (%) of compound released was 1.32% and 1.41% for Pfizer Docetaxel Injection Concentrate, and Taxotere®, respectively.
 - Conclusions
 - Under the conditions tested, Pfizer Docetaxel Injection Concentrate and Taxotere® exhibit similar properties in plasma protein binding and *in vitro* release of docetaxel from micelles.

6 General Toxicology

Pfizer did not conduct any general toxicology studies in support of this NDA submission.

7 Genetic Toxicology

Pfizer did not conduct any genetic toxicology studies in support of this NDA submission.

8 Carcinogenicity

Pfizer did not conduct any carcinogenicity studies in support of this NDA submission.

9 Reproductive and Developmental Toxicology

Pfizer did not conduct any reproductive and developmental toxicology studies in support of this NDA submission.

9 Special Toxicology Studies

10 None.

11 Integrated Summary and Safety Evaluation

Pfizer submitted this New Drug Application (NDA) for Docetaxel Injection Concentrate, 10 mg/mL, as a 505(b)(2) application, for the same clinical indications (breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer), route of administration, dosages, and dosing schedule as Taxotere[®], the reference listed drug (RLD). Studies conducted by Pfizer have shown that Pfizer Docetaxel Injection Concentrate does not contain novel impurities or degradants when compared to Taxotere. All excipients in the Pfizer Docetaxel Injection Concentrate drug product are listed in the FDA Inactive Ingredient Database and are present in other FDA-approved drug products used by the intravenous infusion route of administration. Nonclinical studies provided in this NDA submission showed that Pfizer Docetaxel Injection Concentrate and Taxotere[®] exhibit comparable pharmacokinetic properties in dogs, and exhibit similar plasma protein binding and docetaxel release from micelles, *in vitro*. However, the applicant has provided inadequate scientific justification for the levels of impurities proposed in this NDA submission. The proposed acceptance criteria for all identified impurities in the Pfizer Docetaxel Injection Concentrate drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit should be lowered to either meet the current ICH Q3B(R2) Guidance or not to exceed the levels detected in Taxotere[®]. Alternatively, data from nonclinical studies to qualify the safety of the levels of these impurities may be required, or their safety adequately justified based on literature citations. This issue needs to be addressed before this NDA can be recommended for approval.

12 Appendix/Attachments

References

1. Bissery et al. Anti-cancer Drugs (1995); 6: 339-368.

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/s/

HAW-JYH CHIU
01/25/2012

ANNE M PILARO
01/26/2012

I concur with the reviewer's conclusion that this 505(b)(2) application is not approvable at the present time, and that a Complete Response (CR) letter should be issued to the Applicant describing the deficiencies and what is needed to correct them for approval. I also concur with the reviewer's recommendation to conduct an additional nonclinical toxicology study/studies to qualify the levels of the impurities and/or degradants that patients would be exposed to if they were present at the acceptance limits proposed by the Applicant. Note to the RPM: The reviewer has included a nonclinical deficiency comment in Section 1.3.2, page 5 of this review to be conveyed to the Applicant in the CR letter.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202356

Applicant: Pfizer Inc.

Stamp Date: April 29, 2011

Drug Name: Docetaxel
Injection Concentrate,
10 mg/mL

NDA Type: 505(b)(2)

On **initial** overview of the NDA application 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?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
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)?	X		
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).			Not applicable.
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 <u>submitted</u> a rationale to justify the alternative route?			Not applicable. Pfizer did not conduct any toxicology studies by the intended human exposure route in support of this 505(b)(2) NDA application.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable. Pfizer did not conduct any pivotal pharm/tox studies.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
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?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Pfizer did not identify any unique impurities above the reporting threshold listed in the ICH Q3B guidance when compared to the reference listed product, Taxotere [®] . The adequacy of the justification for the proposed impurity specifications will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?		X	Not applicable.
12	If this NDA 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.

Haw-Jyh Chiu, Ph.D. June 1, 2011

 Reviewing Pharmacologist Date

Anne M. Pilaro, Ph.D. June 1, 2011

 Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

HAW-JYH CHIU
06/01/2011

ANNE M PILARO
06/02/2011

I concur with the reviewer's conclusion that the nonclinical sections of the NDA support filing of this application. No additional action is indicated at the present time from the nonclinical discipline.