CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	202356/SDN 19, 20, 21
Submission Date:	9/13/2013, 11/05/2013, 1/10/2014
Brand Name:	Docetaxel Injection Concentrate™
Generic Name:	Docetaxel
Formulation:	10 mg/mL
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Predictive Safety Reviewer:	Darrell R. Abernethy, MD, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Pfizer
Submission Type; Code:	Complete Response and labeling supplement
Dosing regimen:	IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m^2, Non-small cell lung cancer: 75 mg/m^2, Prostate cancer: 75 mg/m^2, Gastric adenocarcinoma: 75 mg/m^2, Head and Neck Cancer: 75 mg/m^2.
Indication:	Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer and gastric adenocarcinoma, head and neck cancer.

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1. Executive Summary

A FDA Complete Response (CR) Letter was issued on 2/14/13 in which the applicant was requested to address potential clinical safety concerns regarding the quantity of ethanol and propylene glycol in the proposed formulation. To address the CR letter, the sponsor submitted the current Resubmission Class 2. The current submission contains new Clinical Pharmacology information and labeling to address potential safety concerns regarding ethanol and propylene glycol present in the proposed docetaxel formulation.

The FDA ONDQA-Biopharmaceutics review team recommended approval for the original NDA submission, based on the acceptability of the Applicant's request to waive the *in vivo* bioequivalence study requirement (DARRTS review 12/23/11). The drug product formulation in the current resubmission is identical to the drug product formulation in the original NDA, and therefore the request to waive the *in vivo* bioequivalence study requirement remains acceptable.

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this NDA to support a recommendation of approval of Docetaxel Injection Concentrate from a clinical pharmacology perspective.

1.1 PHASE IV COMMITMENTS

None.

1.2 REGULATORY BACKGROUND

The original submission for the current 505(b)(2) application was reviewed previously by the Office of Clinical Pharmacology (NDA 202356/000; letter date: 04/29/2011). Based on the original review, the original submission was found to be acceptable from a clinical pharmacology perspective. However, due to nonclinical and product quality issues identified during the original review, FDA issued a Complete Response letter on 02/29/2012. The applicant resubmitted their application (SDN 12, 13; letter date 08/14/12 and 08/31/12). However, additional issues were identified.

A FDA Complete Response (CR) Letter was issued on 2/14/13 requesting the applicant to address potential clinical safety concerns regarding the quantity of ethanol and propylene glycol in the proposed formulation as follows:

> *FDA: The combination of ethanol and propylene glycol in this proposed docetaxel formulation may result in an increase in the toxicity of your docetaxel product compared to that of the reference drug (Taxotere®). The magnitude of the potential increase in toxicity and the potential difference in toxicity profiles between your docetaxel product and the referenced drug remains uncertain without additional clinical information. Please provide additional information to better characterize potential alcohol-related toxicities. This information could include one of the following:*
> *a. Published references that enable adequate estimation of the toxicity expected from:*
> *i. the amount of ethanol used in your product*
> *ii. the extent to which propylene glycol adds to ethanol intoxication; and*
> *iii. the potential interaction between these two agents (e.g. competition for alcohol dehydrogenase)*

To address the CR letter dated 2/14/13, the sponsor submitted the current Resubmission. The following is a review of the relevant Clinical Pharmacology information submitted to address potential safety concerns regarding ethanol and propylene glycol present in the proposed docetaxel formulation. The current submission does not contain changes to the Clinical Pharmacology labeling previously reviewed by FDA clinical pharmacology reviewer (SDN 12, 13).

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The Predictive Safety Team in OCP was consulted for this review. This section reflects findings from both the DCP5 review team and the Predictive Safety Team.

The total ethanol dose and estimated end-of infusion blood ethanol concentration (C_{max}) were higher for Docetaxel Injection than the listed drug (Taxotere 1-vial formulation) or the Taxotere 2-vial formulation. The total ethanol dose and predicted end-of-infusion blood ethanol concentration following a maximum 200 mg dose of Docetaxel Injection were 6.4 g and 15 mg/dL, respectively. Based on published literature on the concentration-effect profile of ethanol, the predicted end-of-infusion blood ethanol concentration (15 mg/dL) may produce mild symptoms of ethanol intoxication, and is below the legal blood alcohol concentration limit for driving. The predicted end-of-infusion blood ethanol concentration (15 mg/dL) following administration of Docetaxel Injection is similar to the 12.5 mg/dL concentration not to exceed in children recommended by the European Medicines Agency (EMA, 2010).

The total propylene glycol dose following a maximum 200 mg dose of Docetaxel Injection is 7.5 g. Propylene glycol may produce CNS depressant effects similar to ethanol; however it is estimated to be one-third as intoxicating as ethanol. The 7.5 g total dose of propylene glycol following a single 200 mg dose of Docexel Injection appears below the threshold of concern, as propylene glycol induced CNS depression appeared to be associated with multiple-day propylene glycol dosing regimens using similar or higher total propylene glycol doses, and not single doses. Based on the estimated end-of infusion blood ethanol and propylene glycol concentrations following Docetaxel Injection, and the Km values for ethanol and propylene glycol at alcohol dehydrogenase (ADH), pharmacokinetic drug interactions resulting in further elevations in blood ethanol or propylene concentrations are not likely.

The labeling language proposed by the applicant adequately addresses potential safety risks of alcohol associated CNS effects, and (b) (4)

Signatures:

Reviewers: Jeanne Fourie Zirkelbach, PhD; Darrell R. Abernethy, MD, PhD
Division of Clinical Pharmacology 5 and Predictive Safety Team

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

Cc: DDOP: CSO - M Fagbami; MTL - E Maher; MO - W Pierce,
DCP- Reviewers - J Fourie Zirkelbach, DR Abernethy

5: DDD - B Booth
DD - A Rahman

1 QUESTION BASED REVIEW

2.1 WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG SUBSTANCE AND THE FORMULATION OF THE DRUG PRODUCT AS THEY RELATE TO CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW?

Pfizer Docetaxel Injection (Docetaxel Injection) 10mg/mL is a reformulation of the reference product Taxotere®. Preparation of Taxotere® for administration is a 2-step process. It is supplied as a 2-component system that includes one vial containing docetaxel injection concentrate and a second vial containing a diluent. The active pharmaceutical ingredient is docetaxel (anhydrous) instead of docetaxel (trihydrate) used in Taxotere®. Docetaxel Injection 10 mg/mL contains the following list of excipients: (b)(4)% v/v polysorbate 80, 40% v/v ethanol, (b)(4)% v/v propylene glycol, 0.01 mg/ml disodium edetate, and approximately 3.5 mg/mL of citric acid (anhydrous). The formulations of Taxotere® and Pfizer Docetaxel Injection 10 mg/mL are compared in Table 1 and Table 2.

Qualitative formulation: Comparison between Taxotere® and Pfizer Docetaxel Injection (10mg/mL solution)

Name of ingredients	Taxotere®	Pfizer Docetaxel Injection
Docetaxel	10mg/mL (when the two components have been reconstituted)	10mg/mL
Polysorbate-80	(b)(4)%v/v	(b)(4)%v/v
Propylene glycol	-	(b)(4)%v/v
Disodium edetate	-	0.01mg/mL
Ethanol	(b)(4)%v/v	40%v/v
Anhydrous citric acid	-	(b)(4) (b)(4) 3.5mg/mL)
Water for injections	(b)(4)%v/v	-

Note that the formulation of Taxotere® is as detailed in both the US Prescribing Information and EU Summary of Product Characteristics.

Qualitative formulation: Comparison between Taxotere® and Pfizer Docetaxel Injection (0.74mg/mL admixture solution)

Name of ingredients	Taxotere®	Pfizer Docetaxel Injection
Docetaxel	0.74mg/mL	0.74mg/mL
Polysorbate-80	(b)(4)%v/v[1]	(b)(4)%v/v[2]
Propylene glycol	-	(b)(4)%v/v
Disodium edetate	-	(b)(4)µg/mL
Ethanol	(b)(4)%v/v	(b)(4)%v/v
Anhydrous citric acid	-	(b)(4)mg/mL
Water for injections	(b)(4)%v/v	(b)(4)%v/v

Other Excipient(s): Include 0.9%w/v sodium chloride, or 5%w/v glucose, for both Taxotere and Pfizer Docetaxel Injection, depending on the choice of admixture diluent.

1 Equivalent to (b)(4)

2 Equivalent to (b)(4)

The current formulation contains propylene glycol not found in the listed drug formulation or any other approved docetaxel for injection 505(b)(2) application. In addition, the alcohol content in the current formulation is higher than that in the listed drug formulation or any other approved docetaxel for injection 505(b)(2) application. In the current submission, the applicant characterized the potential for intoxication due to ethanol and/or propylene glycol and comparability of the current formulation with the listed drug (see Regulatory Background above).

Product	Ethanol (g)*	Propylene Glycol (g)*
Docetaxel Injection (Pfizer)	6.4	7.5
Taxotere 1-vial (listed drug)	(b) (4)	0
Taxotere 2-vial	(b) (4)	0

**Assumes maximum dose of 100 mg/m^2, BSA = 2.0 m^2, 200 mg dose administered*

2.2 WHAT ARE THE DESIGN FEATURES OF THE CLINICAL PHARMACOLOGY AND CLINICAL STUDIES USED TO EVALUATE THE POTENTIAL CLINICAL SAFETY CONCERNS?

To evaluate the potential for docetaxel injection to elicit clinical signs of intoxication, the applicant submitted pharmacokinetic simulations for ethanol and propylene glycol following intravenous (IV) infusion at the maximum clinical dose. Predicted propylene glycol concentrations were obtained using data from a published manuscript (Speth et al., 1997)[1]. Predicted alcohol concentrations were obtained using data from four published manuscripts[2] and two standard equations defined below (*Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*, 3rd Ed. J Gabrielsson and D Weiner, Swedish Pharmaceutical Press, Stockholm, Sweden, 2000).

During Infusion Equations:
C = Rin/Cl*[1-exp(-CL/V*t)]
Rin = total intake/infusion duration (g/h)
Css = Rin/Cl
Frac_Css = C/Css = 1-exp(-CL/V*t)
K = Cl/V, Cl =k*V
T1/2 = 0.693/k, k = 0.693/t1/2

Post-Infusion Equations:
C = Rin/Cl*[1-exp(-Cl/V*Tinf)]*exp(-Cl/V*t')
t' = t(total)-Tinf
Rin = total intake/infusion duration (g/h)
Cl = 0.693/t1/2*V(L/h)
V = BW*1*frac total body water (L)

[1]Manuscripts used for predicted propylene glycol concentrations:

1 Speth PA et al., Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit 1987:9(3):255-8.

[2]Manuscriptdata used for predicted alcohol concentrations:

1 Jones AW et al., Pharmacokinetics of ethanol in plasma and whole blood: estimation of total body waster by the dilution principle. Eur J Clin Pharmacol 1992;42(4):445-8.

2 Jones AW et al., Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J Forensic Sci 1997;42(6)Nov:1088-94.

3 Rangno RE et al., Ethanol 'dose-dependent' elimination: Michaelis-Menten v classical kinetic analysis. Br J Clin Pharmacol 1981;12(5):667-73.

4 Yoshihara et al., The effects of the ALDH2*1/2, CYP2E1 C1/C2 and C/D genotypes on blood ethanol elimination. Drug Chem Toxicol 2000:23(2):371-9.

The analysis addressed the following review questions:

1. What is the total ethanol dose administered following Docetaxel Injection compared to Taxotere, and what are the estimated end-of-IV-infusion and 30-minutes post- IV-infusion blood ethanol concentrations of Docetaxel Injection compared to Taxotere?

2. What is the propylene glycol content and estimated end-of-infusion blood propylene glycol concentration following an IV infusion of Docetaxel Injection?

3. What is the influence of genetic/phenotypic variations, metabolic inhibition and renal impairment on end-of-infusion blood ethanol/propylene glycol concentrations following administration of Docetaxel Injection?

4. Is there a potential for a pharmacokinetic drug interaction between ethanol and propylene glycol following the IV administration of Docetaxel Injection?

5. Are there safety concerns as a result of ethanol and propylene glycol mediated impairment of psychomotor skills (alcohol intoxication) following a maximum 200 mg dose of Docetaxel Injection?

2.3 WHAT IS THE TOTAL ETHANOL DOSE ADMINISTERED FOLLOWING DOCETAXEL INJECTION COMPARED TO TAXOTERE, AND WHAT ARE THE ESTIMATED END-OF-IV-INFUSION AND 30-MINUTES POST- IV-INFUSION BLOOD ETHANOL CONCENTRATIONS OF DOCETAXEL INJECTION COMPARED TO TAXOTERE?

There was a strong correlation between observed end-of-infusion alcohol concentrations obtained from the literature referenced above and the predicted end-of-infusion blood ethanol concentrations using standard formula described above (Figure 1).

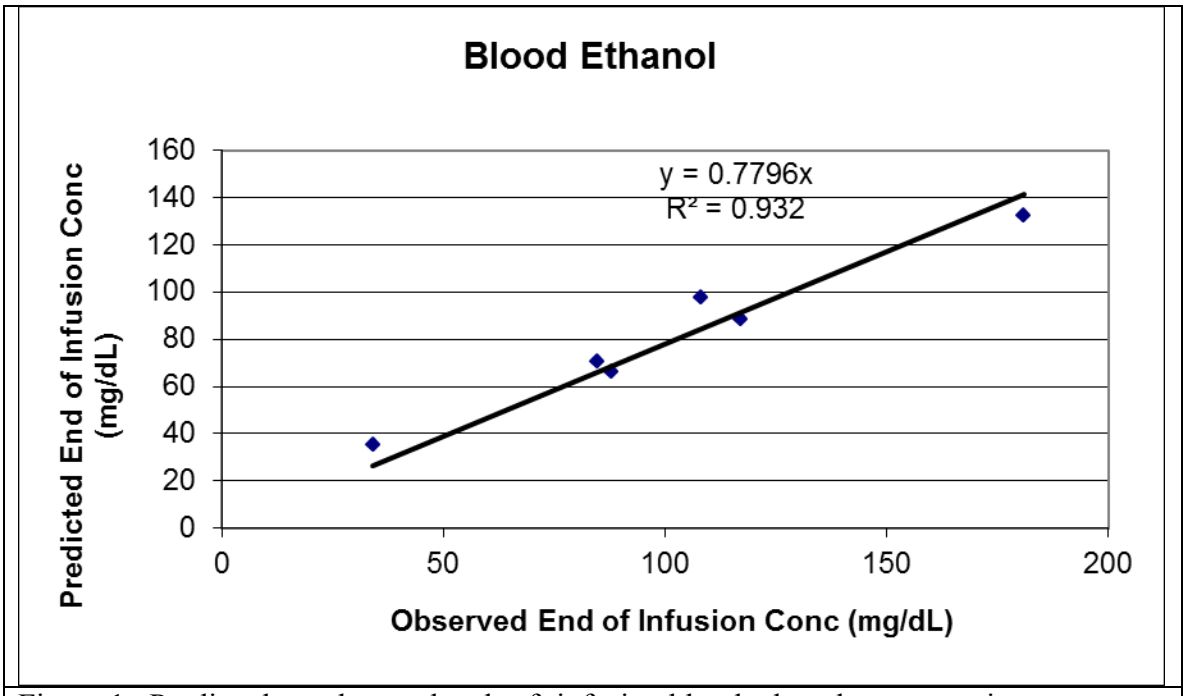

Figure 1. Predicted vs. observed end- of- infusion blood ethanol concentrations.

A comparison of total dose of ethanol and estimated end-of-infusion blood ethanol concentration following administration of a maximum dose of Docetaxel Injection or Taxotere is provided in Table 2. The total dose of ethanol from Docetaxel Injection is 6.4 g as calculated from the maximum dose of the drug product (100 mg docetaxel anhydrous) per square meter, which equates to 200 mg docetaxel (anhydrous) in 20 mL solution assuming a maximum body surface area of 2 square meters). The dose of ethanol from the listed drug (Taxotere one-vial formulation) is (b) (4) g for the same docetaxel dose, and (b) (4) g for Taxotere two-vial formulation.

Docetaxel is administered as a one-hour infusion every 3 weeks, and peak blood ethanol concentrations would be achieved transiently following the 1-hour infusion, followed by a washout period of three weeks.

Overall, the total dose and estimated end-of infusion ethanol concentrations were higher for Docetaxel Injection vs. the listed drug (Taxotere 1-vial formulation) or the Taxotere 2-vial formulation.

Table 2. Ethanol Total Dose and End-of-Infusion blood Ethanol Concentrations Following Infusion of Docetaxel Injection and Taxotere (200 mg maximum Docetaxel Dose).

	Ethanol Elimination half-life (h)	**Total Dose Ethanol (g)**	**Blood Ethanol Conc. At the End-of-Infusion (estimated) (mg/dL)**
Docetaxel Injection	2	6.4	15
Listed Drug: Taxotere (1-vial formulation)	2	(b) (4)	5

Taxotere (2-vial formulation)	2	(b) (4)	9

Patients may be ready to operate equipment and drive home at approximately 30 minutes following the 1-hour IV infusion of Docetaxel Injection. Therefore, the blood concentration of ethanol at 30-minutes post-infusion was estimated to characterize the safety risk and potential for CNS effects related to alcohol. The equation referenced above for calculating post-infusion concentrations was used to predict the blood concentrations of ethanol at 30 minutes post-infusion at different assumed elimination half-lives (Table 3). These half-lives were 2-fold shorter t1/2 = 1-hour) or longer (t1/2 = 4-hours) than the 2-hour estimate from the four publications above[2].

Table 3. Estimated Ethanol Blood Concentrations at the End-of Infusion and at 30-Minutes Post-1-Hour Infusion of Docetaxel Injection (200 mg maximum Docetaxel Dose)

Ethanol Elimination half-life (h)	**Blood Ethanol Conc. At the End-of-Infusion (Estimated) (mg/dL)**	**Blood Ethanol Conc. At 30 Minutes Post-1-Hour-Infusion (Estimated) (mg/dL)**
1	13	9
2	15	13
4	16	15

The estimated blood ethanol concentrations at 30 minutes following the 1-hour intravenous administration of Docetaxel Injection are similar to the end-of-infusion estimated blood alcohol concentrations.

2.4 WHAT IS THE PROPYLENE GLYCOL CONTENT AND ESTIMATED END-OF-INFUSION BLOOD PROPYLENE GLYCOL CONCENTRATION FOLLOWING AN IV INFUSION OF DOCETAXEL INJECTION?

The total dose of propylene glycol from Docetaxel Injection at the maximum (200 mg docetaxel) dose is 7.5g. The applicant predicted the end-of-infusion blood concentration of propylene glycol following a 1-hour IV infusion of Docetaxel Injection based on published data (Speth et al., 1987)[1]. Speth and colleagues reported a half-life of 2.3 hours with a range of 1.4 to 3.3 hours. Both the 1.4 hour and 3.3 hour half-lives were considered for the prediction of the end-of-infusion blood concentration of propylene glycol (Table 5).

Table 5. Estimated Propylene Glycol Blood Concentrations at the End-of Infusion and at 30-Minutes Post-1-Hour Infusion (200 mg Docetaxel Dose).

Propylene Glycol Elimination half-life (h)	**Blood Propylene Glycol Conc. At the End-of-Infusion (Estimated) (mg/dL)**
1.4	10.8
3.3	12.4

2.5 WHAT IS THE INFLUENCE OF GENETIC/PHENOTYPIC VARIATIONS, METABOLIC INHIBITION AND RENAL IMPAIRMENT ON END-OF-INFUSION BLOOD ETHANOL/PROPYLENE GLYCOL CONCENTRATIONS FOLLOWING ADMINISTRATION OF DOCETAXEL INJECTION?

Ethanol is metabolized via a simple oxidative pathway, mainly in the liver. Over 90% of ethanol absorbed from the gut is catabolized via the pathways shown in Figure 2 but wide variations are observed in the overall rate of ethanol oxidation, because of the occurrence of a number of genetic variants of the enzymes involved. The remainder is eliminated in unchanged form, in breath, sweat and urine.

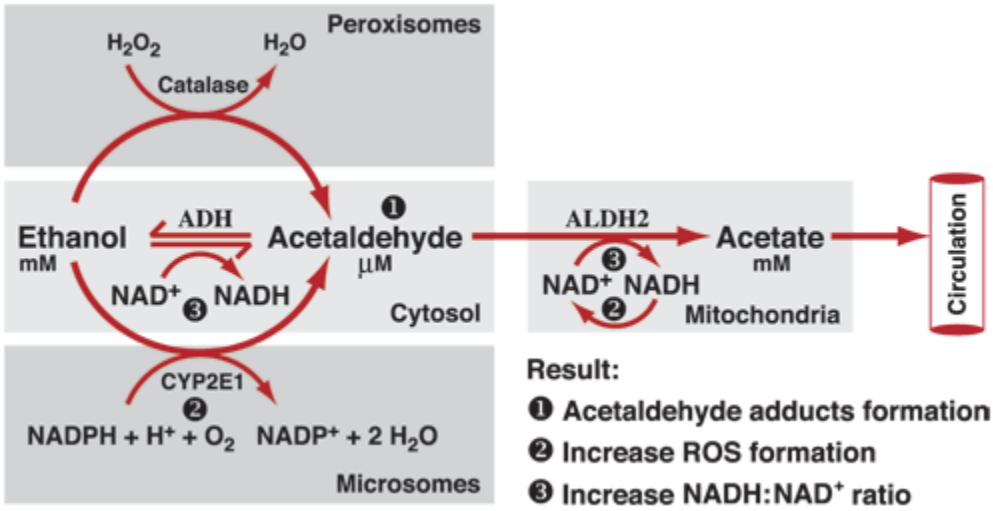

Figure 2: Oxidative pathways of alcohol metabolism. The enzymes alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and catalase all contribute to oxidative metabolism of alcohol.

Genetic and phenotypic variations in ethanol metabolism occur among different ethnic populations, and could result in variations in the end-of-infusion blood ethanol concentrations following infusion of Docetaxel Injection. Based on the data from the publications above[2] the assumed elimination half-life for ethanol was 2 hours. In order to address the potential impact of these genetic/phenotypic variations, end-of-infusion ethanol concentrations were calculated based on ethanol elimination half-lives that were 2-fold shorter t1/2 = 1-hour) or longer (t1/2 = 4-hours) than the 2 hour estimate from the four publications above[2]. The end-of-infusion ethanol concentrations at the 1-hour, 2-hour and 4-hour elimination half-lives were 13, 15 and 16 mg/dL, respectively, following infusion of Docetaxel Injection (Table 3). These assumptions of shorter and longer ethanol elimination half-lives could not be verified with data from the literature.

Clearance of propylene glycol would be influenced by renal function and ethanol-mediated inhibition of ADH, and these factors were considered by the applicant in the estimation of end-of-infusion blood propylene glycol concentrations. Propylene glycol clearance is reported to be partially mediated (25-45%) by renal clearance (Kraut and Kurtz, 2008) and some patients receiving Docetaxel Injection may exhibit varying degrees of renal insufficiency. Based on these

considerations, the end-of-infusion propylene glycol concentrations were predicted under three conditions by the applicant: 1) as if no metabolic inhibition by ethanol occurred, 2) assuming only metabolic and no renal clearance (CLr) in individuals with limited kidney function, and 3) assuming ethanol further inhibited metabolic clearance by 90%. These results are summarized in Table 4.

Table 4. Influence of Metabolic Inhibition and Renal Impairment on End-of-Infusion Blood Propylene Glycol Concentrations Following Infusion of Docetaxel (200 mg Docetaxel Dose).

Estimated End-of-Infusion Blood Propylene Glycol Concentration (mg/dL)		
No Metabolic Inhibition or Renal Impairment	Metabolic Inhibition with Renal Clearance	Metabolic Inhibition with Renal Impairment
10.8	12.4	13.7

The predicted end of infusion propylene glycol concentrations ranged from approximately 11 to 14 mg/dL for the three conditions. Based on the dosing regimen for docetaxel of a 1-hour infusion once every three weeks, it is estimated that that ethanol-mediated inhibition of ADH and/or renal impairment will have a minor impact on the propylene glycol blood concentration.

2.6 IS THERE A POTENTIAL FOR A PHARMACOKINETIC DRUG INTERACTION BETWEEN ETHANOL AND PROPYLENE GLYCOL FOLLOWING THE IV ADMINISTRATION OF DOCETAXEL INJECTION?

The potential for propylene glycol present in the Docetaxel Injection formulation to inhibit the metabolism of ethanol was evaluated by the applicant. Propylene glycol is reported to have a 20-fold higher Km for alcohol dehydrogenase (ADH) than ethanol (Kraut and Kurtz, 2008)[3]. As described further below, the predicted end-of-infusion blood propylene glycol concentrations from Docetaxel Injection would not be predicted to result in further elevations in blood ethanol concentrations.

Ethanol may reduce the metabolic clearance of propylene glycol through inhibition of ADH. The blood ethanol concentration estimated to cause complete inhibition of ADH of 100 mg/dL (Kraut and Kurtz, 2008) is substantially higher than the estimated peak concentration reached following administration of Docetaxel Injection (15 mg/dL).

[3]Kraut and Kurtz. Toxic alcohol ingestions: Clinical features, diagnosis and management. Clin J AM soc Nephrol 2008;3(1):208-25.

2.7 ARE THERE SAFETY CONCERNS AS A RESULT OF ETHANOL AND PROPYLENE GLYCOL MEDIATED IMPAIRMENT OF PSYCHOMOTOR SKILLS (ALCOHOL INTOXICATION) FOLLOWING A MAXIMUM 200 MG DOSE OF DOCETAXEL INJECTION?

The total ethanol dose and predicted end-of-infusion blood ethanol concentration following a maximum 200 mg dose of Docetaxel Injection were 6.4 g and 15 mg/dL (0.015%),respectively. Based on published literature, blood ethanol concentrations > 100 mg/dL are known to result in impairment of motor function, which includes altered perception, ataxia, impaired judgment, lack of coordination, mood, personality, and behavioral changes, nystagmus, prolonged reaction time and slurred speech. Blood ethanol concentrations > 50 mg/dL are associated with impairment of some tasks requiring skill, increased talkativeness and increased relaxation. A blood ethanol concentration of 40 mg/dL is considered the threshold for negative effects on psychomotor tasks, and is associated with significant effects on subjective and performance measures. A blood ethanol concentration of >10 mg/dL is associated with increased stimulation and the "feeling of intoxication" threshold. Therefore, the predicted end-of-infusion blood ethanol concentration (15 mg/dL) following a single 200 mg dose of Docetaxel Injection may produce mild CNS depression, and is below the legal blood alcohol concentration limit for driving.

The European medicines agency (EMA, 2010) has published that ethanol content in herbal medicines used in children should not exceed a blood ethanol concentration of 12.5 mg/dL following a single dose. This recommendation is based on the impairment of psychomotor skills that can occur with blood ethanol concentrations > 12.5 mg/dL. The end-of-infusion blood ethanol concentration (15 mg/dL) following administration of a 200 mg maximum dose of Docetaxel Injection is similar to the 12.5 mg/dL concentration not to exceed in children recommended by the EMA. (b) (4)

The total propylene glycol dose following a maximum 200 mg dose of Docetaxel Injection is 7.5 g. Propylene glycol may produce CNS depressant effects similar to those of ethanol; however it is estimated to be one-third as intoxicating as ethanol (Tran et al, 2007; Rowe et al, 2012). A consult was issued to the Predictive Safety Team in OCP to further address potential safety concerns that could be associated with the ethanol and propylene glycol blood concentrations estimated following a maximum 200 mg dose of Docetaxel Injection administered as a 1-hour intravenous injection. Conclusions reached by the Predictive Safety Team were similar to those from the reviewer (See Appendix). In brief, the consult concluded that the 7.5 g total dose of propylene glycol following a single 200 mg dose of Docexel Injection appears below the threshold of concern, as CNS effects (CNS depression) appear to be associated with multiple-day dosing regimens using similar or higher total doses of propylene glycol and not single doses (See Appendix).

Tran MN, Wu AH, Hill DW. Alcohol dehydrogenase and catalase content in perinatal infant and adult livers: potential influence on neonatal alcohol metabolism. Toxicol Lett 2007; 169(3):245-52.

Rowe RC, Sheskey PJ, Cook WG, et al. Propylene glycol. In: Rowe RC, Sheskey PJ, Cook WG, editors. Handbook of Pharmaceutical Excipients. 7th ed. London: Pharmaceutical Press; 2012: p. 407-8.

3.0 LABELLING

The following changes to the current Taxotere label were proposed by the applicant to address safety concerns due to the addition of alcohol and propylene glycol in the proposed formulation (underlined):

5.8 Neurologic Reactions

Severe neurosensory symptoms (e.g., paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued *[see Dosage and Administration (2.7)]*. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

(b) (4)

5.12 Alcohol Content

(b) (4)

4.0 APPENDIX: PREDICTIVE SAFETY TEAM REVIEW

January 10, 2014

To: Jeanne Fourie Zirkelbach
Qi Liu

From: Darrell R. Abernethy, Predictive Safety Team

Re: Docetaxel NDA 20356

Thank you for contacting us about this interesting issue regarding the potential toxicity of the ethanol and propylene glycol excipients in Docetaxel (Pfizer), NDA 20356. I have reviewed the materials you sent, including portions of the NDA, and the slide set from William Pierce.

First, the slide set summarizes the issue very nicely, and is very helpful in formulating the issue. I will attempt to answer some of the specific questions you raise.

1. *Is the difference in the amount of alcohol present in the Pfizer formulation vs Taxotere or the Sandoz formulation likely to cause a clinically significant safety difference?* There would be little difference between the Pfizer formulation and the Sandoz formulation, as the ethanol exposure is quite similar. There may well be a clinically significant safety difference between the Pfizer formulation and Taxotere.

   The contribution of propylene glycol to CNS depression is generally believed to be about 1/3 that of ethanol, and both propylene glycol and ethanol are significantly metabolized by alcohol dehydrogenase. The ethanol blood concentrations achieved at the end of the infusion (the 15mg/dL indicated in the slides seems a reasonable guess) are well above the Km for ethanol (3-9 mg/dL), so at this concentration, the metabolic elimination will be zero order, however the metabolic elimination of propylene glycol will be first order as its Km is about 10 fold higher than that of ethanol. Therefore it is unlikely there will be a significant slowing of ethanol metabolic elimination due to the presence of this concentration of propylene glycol. Ethanol Vmax for a 70kg individual is in the range of 5-7g/h/70kg (1). Therefore, ½ hour following the end of the infusion (distribution equilibrium would be achieved with the 30 minute infusion), the ethanol blood concentration may be in the range of 7-10 mg/dL. This is a concentration that the patient may well have mild CNS impairment, and it is important to note that there is marked interindividual variation, such that some individuals may have no significant impairment, and others may have greater impairment.

2. *How high can the amounts of alcohol and propylene glycol increase in formulations before there is a safety concern?* As noted above, the 6.4 gram dose of ethanol over 30 minutes may well be at that threshold of concern. For propylene glycol, the 7.5 gram single dose is certainly below a threshold of concern for an adult. The CNS effects of propylene glycol are much less quantitatively understood than for ethanol. Clearly at very high doses or with prolonged daily administration at lower doses (eg 7.7 grams/day for 8 days in a 15 month old child (2)) , marked CNS depression and metabolic effects can occur. The instances in which propylene glycol toxicity in association with drug administration have been reported have generally been with prolonged (many days) infusion of lorazepam, or other drugs in which propylene glycol is the major excipient and the dose and duration of exposure is high. Therefore it is difficult to have a clear opinion about the amount of propylene glycol that is likely to cause CNS toxicity with a single dose or infusion. Some insight is gained in a study that administered 40 grams of propylene glycol every 8 hours for 3 days to patients with seizure disorders (3). Here some individuals were said to have CNS toxicity (not quantified, just a casual observation in a pharmacokinetic study).

3. *If the current Pfizer formulation is approved, what approaches should be taken to decrease the safety risks?* I believe that a warning about potential sedation and impairment in psychomotor function for 1-2 hours following completion of the infusion would be appropriate.

References:

1. Holford NHG: Clinical pharmacokinetics of ethanol. Clin Pharmacokinet 1987;13:273-292.
2. Martin G, Finberg L: Propylene glycol: A potentially toxic vehicle in liquid dosage form. J Pediatr 1970;77:877-878.
3. Yu DK, Elmquist WF, Sawchuk RJ: Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. J Pharm Sci 1985;74:876-879.

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/s/

JEANNE FOURIE ZIRKELBACH
01/24/2014

DARRELL R ABERNETHY
01/27/2014

QI LIU
01/28/2014

NDA FILING AND REVIEW FORM

Office of Clinical Pharmacology			
General Information About the Submission			
NDA Number	NDA 202356	**Brand Name**	Docetaxel Injection Concentrate®
OCP Division	DCP V	**Generic Name**	docetaxel
OND Division	DOP1	**Drug Class**	Microtubule inhibitor
OCP Reviewer	Jeanne Fourie Zirkelbach, Ph.D.	**Indication(s)**	Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck,
OCP Team Leader	Qi Liu, Ph.D.	**Dosage Form**	Docetaxel Injection Concentrate 10 mg/mL: · 20 mg/2 mL · 80 mg/8 mL · 130 mg/13 mL · 200 mg/20 mL
Sponsor	Pfizer	**Route of Administration**	IV infusion
Date of Submission	09/12/13	**Priority Classification**	Resubmission – Complete Response
PDUFA Due Date			

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Metabolic profiling				
Isozyme characterization:				
Active Metabolites				
Transporters				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
Healthy volunteers				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
Drug-drug interaction studies				
In-vivo effects on primary drug:				

In-vivo effects of primary drug on other drugs:				
In-vitro:				
Subpopulation studies -				
Body size				
gender:				
geriatrics:				
renal impairment:				
Race/Ethnicity:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QT_C studies				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	x	1		Analysis of published literature.
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	19		19 articles to support the complete response to the FDA clincial query.
Total Number of Studies				

CC: DHP: (CSO – M Fagbami; MTL –E Maher; MO –W Pierce)
OCP: (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD-B Booth; DD - A Rahman)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			Data speadsheet requested as IR.
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology 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: N/A

Clinical Pharmacology - NDA Filing Memo

BLA: 20356\0 Resubmission – Complete Response
Compound: Docetaxel Injection Concentrate
Sponsor: Pfizer
Filing Date: Oct 31, 2013
Reviewer: Jeanne Fourie Zirkelbach, PhD

In the current resubmission, the sponsor provided a response to the previous FDA query communicated in the FDA Complete Response Letter (February 14, 2013) below. The response consists of literature references and analysis of published data to address the following FDA query.

FDA QUERY
CLINICAL
The combination of ethanol and propylene glycol in this proposed docetaxel formulation may result in an increase in the toxicity of your docetaxel product compared to that of the reference drug (Taxotere). The magnitude of the potential increase in toxicity and the potential difference in toxicity profiles between your docetaxel product and the referenced drug remains uncertain without additional clinical information. Please provide additional information to better characterize potential alcohol-related toxicities. This information could include one of the following:
a. Published references that enable adequate estimation of the toxicity expected from:
i. the amount of ethanol used in your product
ii. the extent to which propylene glycol adds to ethanol intoxication; and
iii. the potential interaction between these two agents (e.g. competition for alcohol dehydrogenase)

b. Results from a clinical trial to assess the safety of your docetaxel product. A trial to assess the toxicity of ethanol and propylene glycol in combination, at amounts similar to those in your product may be acceptable if combined with adequate safety monitoring and assessment strategies for alcohol-related toxicities. The design of such a study should account for variability in expression of toxicity in patients in response to a given blood alcohol level. Should you choose to proceed with such a trial, we advise that you submit a protocol for our review.

c. A reformulation of your docetaxel product to deliver ethanol and propylene glycol at amounts (individually or in combination) that are not higher than other docetaxel products.

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/s/

JEANNE FOURIE ZIRKELBACH
12/16/2013

QI LIU
12/16/2013

Clinical Pharmacology Review

NDA	202356/SDN 12, 13
Submission Date:	8/14/2012, 8/31/2012
Brand Name:	Docetaxel Injection Concentrate™
Generic Name:	Docetaxel
Formulation:	10 mg/mL
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Pfizer
Submission Type; Code:	Complete Response and labeling supplement
Dosing regimen:	IV over 1 hr every 3 weeks. Breast Cancer: 60-100 mg/m^2, Non-small cell lung cancer: 75 mg/m^2, Prostate cancer: 75 mg/m^2, Gastric adenocarcinoma: 75 mg/m^2, Head and Neck Cancer: 75 mg/m^2.
Indication:	Breast cancer, non-small cell lung cancer, hormone refractory prostate cancer and gastric adenocarcinoma, head and neck cancer.

Table of contents

1 EXECUTIVE SUMMARY

The original submission for the current application was reviewed previously by the Office of Clinical Pharmacology (NDA 202356/000; letter date: 04/29/2011). Based on the original review, the submission was found to be acceptable from a clinical pharmacology perspective. The current review summarizes the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 202356 (SDN 12, 13). This submission is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 2 - Detailed Labeling Recommendations.

1.2 PHASE IV COMMITMENTS

None.

1.3 REGULATORY BACKGROUND

The original submission for the current 505(b)(2) application was reviewed previously by the Office of Clinical Pharmacology (NDA 202356/000; letter date: 04/29/2011). Based on the original review, the original submission was found to be acceptable from a clinical pharmacology perspective. The original review did contain labeling recommendations. FDA issued a Complete Response letter on 02/29/2012 with nonclinical and product quality issues identified during the original review. The current submission consists of the response to the Complete response letter and updated proposed labeling for Docetaxel Injection Concentrate™. The proposed labeling is based on the most recently approved label for the two-vial formulation of Taxotere™ (listed drug, NDA 20449, December, 2011).

The response to the Compete Response Letter did not contain any new Clinical Pharmacology Data. The purpose of the current review is to summarize the relevant Clinical Pharmacology labeling recommendations for this 505(b)(2) application.

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD Division of Clinical Pharmacology 5	Team Leader: Qi Liu, PhD Division of Clinical Pharmacology 5

Cc: DDOP: CSO - ; MTL - E Maher; MO - W Pierce,
DCP-5: Reviewers - J Fourie Zirkelbach,
DDD - B Booth
DD - A Rahman

2 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are shown in track change format below. The sponsor's proposed changes from the most recent Taxotere label are shown in underlined text or in yellow highlight. FDA proposed changes are shown in blue text.

RLD Label	Proposed Label for Pfizer's Docetaxel Injection Concentrate	Reviewer's Comments
---------- **DRUG INTERACTIONS**---------- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	----------**DRUG INTERACTIONS**--- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	No change.
FULL PRESCRIBING INFORMATION **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Aoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	**FULL PRESCRIBING INFORMATION** **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	The applicant deleted a period (see yellow highlight) in this section, and this is acceptable.
5.2 Hepatic Impairment Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with TAXOTERE *[see Boxed Warning, Use in Specific Populations (8.6), Clinical Studies (14)]*.	**5.2 Hepatic Impairment** Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate *[see Boxed Warning, Use in Specific Populations*	The applicant changed TAXOTERE to Docetaxel. The reviewer further changed Docetaxel to the full product name, Docetaxel Injection Concentrate.

	(8.6), Clinical Studies (14)].	
7. DRUG INTERACTIONS Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	**7. DRUG INTERACTIONS** Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection Concentrate and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection Concentrate, close monitoring for toxicity and a Docetaxel Injection Concentrate dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	The applicant changed TAXOTERE to Docetaxel. The reviewer further changed Docetaxel to the full product name, Docetaxel Injection Concentrate.
8.4 Pediatric Use Pharmacokinetics: Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2 . Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m2 in a 1-hour intravenous infusion day 1 in 28 patients	**8.4 Pediatric Use** ~~Pharmacokinetics:~~ ~~Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2 . Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion~~	Pediatric Use Section PK data should not be presented in 505(b)(2) applications.

aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg.h/mL. In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.	~~day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg h/mL.~~ ~~In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.~~	
8.6 Hepatic Impairment Patients with bilirubin >ULN should not receive TAXOTERE. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive TAXOTERE *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology* *(12.3)]*.	**8.6 Hepatic Impairment** Patients with bilirubin >ULN should not receive Docetaxel Injection Concentrate. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel Injection Concentrate *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.	Throughout Section 8.6, TAXOTERE is changed by the Applicant to Docetaxel. The FDA reviewer has changed Docetaxel to the full product name Docetaxel Injection Concentrate.
12.3 Human Pharmacokinetics Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m2 to 115 mg/m2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume	**12.3** (b) (4) **Pharmacokinetics** Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral	

of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel. Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. Elimination: A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age. Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not	compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel. Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Effect of Age: A population pharmacokinetic analysis was carried out after ~~Docetaxel~~ docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age. Effect of Gender: The population pharmacokinetics analysis described	The FDA reviewer has changed Docetaxel to docetaxel in the place where the product was evaluated in the clinical trial by the innovator.

influence the pharmacokinetics of docetaxel. Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]* Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m2 to 90 mg/m2 was similar to that of European/American populations dosed at 100 mg/m2, suggesting no significant difference in the elimination of docetaxel in the two populations. Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) incombination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was	above also indicated that gender did not influence the pharmacokinetics of docetaxel. Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate. Patients with severe hepatic impairment have not been studied *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*. Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations. Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of	The FDA reviewer has changed Docetaxel to the full product name, Docetaxel Injection Concentrate. The applicant deleted a period (see yellow highlight) in this section, and this is acceptable. The applicant changed "co-administration" to 'co-administered' as this sentence was not gramatically correct in the label for the innovator product. The FDA reviewer finds this to be acceptable. The applicant changed

co-administration with ketoconazole *[see Dosage and Administration (2.7) and Drug-Drug Interactions (7)]*. Effect of Combination Therapies: • Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone. • Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²),	this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administered with ketoconazole *[see Dosage and Administration (2.7)* and *Drug Interactions (7)]*. Effect of Combination Therapies: • Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone. • Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²),	"Drug-Drug Interactions" to "Drug Interactions", as this is the correct Section title reference. The FDA reviewer finds this change to be acceptable.

doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	

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/s/

JEANNE FOURIE ZIRKELBACH
01/17/2013

QI LIU
01/22/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-356 Resubmission	**Reviewer:** Elsbeth Chikhale, Ph.D.	
Resubmission Date:	August 14, 2012		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Pfizer Inc.	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	TBD	**Date Assigned:**	September 6, 2012
Established Name:	Docetaxel Injection	**Date of Review:**	November 19, 2012
Indication:	Breast Cancer; Non-Small Cell Lung Cancer; Prostate Cancer; Gastric Adenocarcinoma; Head and Neck Cancer	**Type of Submission:** Resubmission of New Drug Application – 505(b)(2)	
Formulation/ strengths	Solution for Injection/ 10 mg/mL		
Route of Administration	IV injection		
Type of Review:	Biowaiver Request		

BACKGROUND:

Original NDA 202-356 for Docetaxel Injection submitted on 4/29/2011 received a "Complete Response (CR)" letter on 2/29/12, mainly due to non-clinical and CMC deficiencies.

SUBMISSION:

On 8/14/12, the resubmission of NDA 202-356 addressing the deficiencies identified in the "Complete Response" letter was submitted. Please note that CR letter did not include any Biopharmaceutics deficiencies or comments. ONDQA-Biopharmaceutics recommended approval for the original NDA during the first review cycle, based on the acceptability of the Applicant's request to waive the *in vivo* bioequivalence study requirement (*see review in DARRTS dated 12/23/11 by Elsbeth Chikhale, Ph.D.*).

RECOMMENDATION:

Since the CR letter did not include Biopharmaceutics deficiencies and the drug product formulation in the NDA's resubmission is identical to the drug product formulation in the original NDA, the request to waive the *in vivo* bioequivalence study requirement remains acceptable. From the Biopharmaceutics perspective, the resubmission of NDA 202-356 for Docetaxel Injection (10 mg/mL) is recommended for APPROVAL.

Signature
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
11/19/2012

ANGELICA DORANTES
11/19/2012

Clinical Pharmacology Review	
NDA	202-356
Submission Type	Original, 505(b)(2)
Submission Date	04/29/2011
PDUFA Date	02/29/2012
Brand Name	Docetaxel Injection Concentrate
Generic Name	Docetaxel
Reference Listed Drug	TAXOTERE (docetaxel) Injection Concentrate
Indications	For the treatment of 1) Breast cancer (BC); 2) Non-small cell lung cancer (NSCLC); 3) Hormone refractory prostate cancer (HRPC); 4) Gastric adenocarcinoma (GC); 5) Squamous cell carcinoma of the head and neck cancer (SCCHN)
Formulation	An intravenous (IV) solution containing 10 mg/mL of docetaxel in single-use vials (20 mg/2 mL; 80 mg/8 mL; 130 mg/13 mL; and 200 mg/20 mL)
Dosing Regimen	IV Infusion over 1 hour every 3 weeks
Sponsor	Pfizer
OCP Reviewer	Lillian H. Zhang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
OCP Division	Division of Clinical Pharmacology 5
Clinical Division	Division of Oncology Products 2 (DOP2)

List of Tables

1 EXECUTIVE SUMMARY

This 505(b)(2) application submitted by Pfizer is for Docetaxel Injection Concentrate, 10 mg/mL in single-dose vials. Pfizer's docetaxel product has the same concentration of the active ingredient, docetaxel (anhydrous), prior to intravenous (IV) administration, the same dosage form, and route of administration as the innovator's drug product, TAXOTERE (docetaxel) Injection Concentrate, approved by the FDA under NDA 20-449 (Sanofi-Aventis). The innovator's TAXOTERE Injection Concentrate is the reference listed drug (RLD) for this 505(b)(2) application.

There is no clinical bioequivalence (BE) study nor any other clinical studies submitted in this application. The Applicant is relying on the findings of safety and effectiveness for TAXOTERE Injection Concentrate to support the approval of their product.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology considers this NDA acceptable from a clinical pharmacology perspective and recommends approval of this application.

For labeling recommendations, please refer to Section 3.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

None.

Signatures:

Lillian H. Zhang, Ph.D. Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - S Sickafuse; MTL - S Lemery; MO - W Pierce
DCP-5: Reviewers - LH Zhang; TL - H Zhao; DDD - B Booth
DD - A Rahman

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Docetaxel is an antineoplastic agent belonging to the taxoid family. TAXOTERE Injection Concentrate, the RLD for this 505(b)(2) application, was approved by the FDA under NDA 20-449 (Sanofi-Aventis) for the following indications:

- *Breast Cancer (BC)*: single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC
- *Non-Small Cell Lung Cancer (NSCLC)*: single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (1.2)
- *Hormone Refractory Prostate Cancer (HRPC)*: with prednisone in androgen independent (hormone refractory) metastatic prostate cancer
- *Gastric Adenocarcinoma (GC)*: with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction
- *Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)*: with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

For all indications, TAXOTERE is recommended to be administered IV over 1 hour every 3 weeks and the recommended dose for each indication is listed below:

- *BC locally advanced or metastatic:* 60 mg/m^2 to 100 mg/m^2 single agent
- *BC adjuvant:* 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles
- *NSCLC after platinum therapy failure:* 75 mg/m^2 single agent
- *NSCLC chemotherapy-naive:* 75 mg/m^2 followed by cisplatin 75 mg/m^2
- *HRPC:* 75 mg/m^2 with 5 mg prednisone twice a day continuously
- *GC:* 75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion
- *SCCHN:* 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion; for 4 cycles; or 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1–4); for 3 cycles

The RLD product is supplied as two-vial formulation (Injection Concentrate and Diluent). Injection Concentrate is a sterile solution and available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80. Injection Concentrate requires dilution with Diluent as the first pre-mix step prior to addition to the infusion bag for further dilution for IV administration. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials. Both Injection Concentrate and Diluent are in a blister pack in one carton.

Pfizer's Docetaxel Injection Concentrate is a solution formulation, containing 10 mg/mL of docetaxel (anhydrous) in single use vials. It does not require a pre-mix step (dilution with a diluent) as the RLD and is ready for further dilution for IV administration. Both the proposed

Pfizer's Docetaxel Injection Concentrate (10 mg/mL) and the initial diluted TAXOTERE solution (10 mg/mL, after the first "pre-mix" step) are further diluted to a 0.74 mg/mL docetaxel (anhydrous) infusion solution, prior to IV administration. Pfizer's Docetaxel Injection Concentrate has the same dosage form and route of administration as the RLD. Even though the starting drug substance for the active ingredient in the proposed Pfizer drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in TAXOTERE, the concentration of the active ingredient, docetaxel (anhydrous), prior to further dilution (10 mg/mL) and after further dilution for IV administration (0.74 mg/mL) is the same for the two products. The difference between the two products is the composition of the inactive ingredients. A comparison of the qualitative and quantitative composition of Pfizer's Docetaxel Injection Concentration (10 mg/mL) with the initial diluted RLD (after the first "pre-mix" step) is presented in Table 1. A comparison of the composition of the final diluted infusion solutions for the two products are presented in Table 2.

Table 1. Formulation Comparison between Pfizer's Docetaxel Injection Concentrate and the Initial Diluted RLD (TAXOTERE)

Ingredients	Pfizer Docetaxel Injection	RLD- TAXOTERE
Docetaxel	10 mg/mL	10 mg/mL (when the two components have been reconstituted)
Polysorbate-80	(b) (4) % v/v	(b) (4) % v/v
Propylene glycol	(b) (4) % v/v	-
Disodium edetate	0.01 mg/mL	-
Ethanol	40% v/v	(b) (4) % v/v
Anhydrous citric acid	(b) (4) (b) (4) 3.5 mg/mL)	-
Water for Injection	-	(b) (4) % v/v

Table 2. Comparison of the Composition of the Final Diluted Infusion Solutions for the Two Products

Ingredients	Pfizer Docetaxel Injection	RLD- TAXOTERE
Docetaxel	0.74 mg/mL	0.74 mg/mL
Polysorbate-80	(b) (4) % v/v	(b) (4) % v/v
Propylene glycol	(b) (4) % v/v	-
Disodium edetate	(b) (4) µg/mL	-
Ethanol	(b) (4) % v/v	(b) (4) % v/v
Anhydrous citric acid	(b) (4) mg/mL	-
Water for Injection	(b) (4) % v/v	(b) (4) % v/v

Other excipients: include 0.9% w/v sodium chloride, or 5% w/v glucose, for both Pfizer Docetaxel Injection and TAXOTERE depending on the choice of admixture diluent.

The Applicant is seeking approval for all the RLD indications. The condition of use and route of administration for the proposed drug product are the same as prescribed and recommended for the use of the RLD.

As both formulations have the same concentration of the active ingredient prior to use, the same dosage form, are intended solely for IV administration, and are true solutions when they are administered to patients, the biopharmaceutics review of this application by the Office of New Drug Quality Assessment (ONDQA) concludes that the Applicant's biowaiver request is acceptable so that the ONDQA has granted a waiver of the BE requirement for Pfizer's Docetaxel Injection Concentrate. The current 505(b)2 application thus does not include any clinical studies and relies on the FDA's findings of safety and effectiveness for the RLD.

2 QUESTION BASED REVIEW

Refer to the RLD original NDA 20-449 (Approval Date: 5/14/96) for any Clinical Pharmacology related issues. For brevity only Question Based Review (QBR) questions related to the current NDA submission are addressed below.

2.1 GENERAL ATTRIBUTITES

2.1.1 What are the proposed dosage and route of administration?

Pfizer's Docetaxel Injection Concentrate is a clear solution and is presented as a single strength (10 mg/mL) in four presentations, containing 20 mg in 2 mL, 80 mg in 8 mL, 130 mg in 13 mL and 200 mg in 20 mL, of docetaxel (anhydrous). Docetaxel Injection Concentrate 10 mg/mL is a single-vial concentrate ready for dilution into a solution and is intended for IV administration.

2.2 GENEARL BIOPHARMACEUTICS

2.2.1 What is the composition of the to-be-marketed formulation?

The components and their functions of Pfizer's proposed Docetaxel Injection Concentrate are provided in Table 3 below:

Table 3. Description of Pfizer's Docetaxel Injection Concentrate 10 mg/mL

Name of Ingredients[1]	Reference to Standards	Function	Quantity per mL[2]
Docetaxel (anhydrous)	Pfizer[3]	Active	10mg
Polysorbate-80 (b) (4)[4]	Ph. Eur. / USP	(b) (4)	259mg
Propylene glycol	Ph. Eur. / USP		374mg
Disodium edetate[5]	Ph. Eur. / USP		0.01mg
Ethanol[6]	Ph. Eur. / USP		(b) (4)
Anhydrous citric acid	Ph. Eur. / USP	pH adjustment	(b) (4) 3.5mg)

2.2.2 What moieties should be assessed in bioequivalence studies?

Refer to Section 1.4 for the comparisons between Pfizer's proposed drug product and the RLD. The concentration of the active ingredient prior to use, dosage form, and route of administration for Pfizer's product are the same as the RLD. A waiver of the bioequivalence requirements for Docetaxel Injection Concentrate is granted by ONDQA in accordance with CFR 320.22 (b). The

current 505(b)2 application thus does not include any clinical studies and relies on the FDA's findings of safety and effectiveness for RLD.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant Clinical Pharmacology sections of the Applicant's proposed label are reproduced below. As a comparison, the Clinical Pharmacology related sections of the RLD label are also included. The changes by the reviewer and the reviewer's comments are in Blue.

RLD Label	Proposed Label for Pfizer's Docetaxel Injection Concentrate	Reviewer's Comments
HIGHLIGHTS OF PRESCRIBING INFORMATION **---------- DRUG INTERACTIONS----------** Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	**HIGHLIGHTS OF PRESCRIBING INFORMATION** **----------DRUG INTERACTIONS----------** Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism. (7)	No change is made.
FULL PRESCRIBING INFORMATION **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	**FULL PRESCRIBING INFORMATION** **2. DOSAGE AND ADMINISTRATION** **2.7 Dosage Adjustments During Treatment** Combination Therapy with Strong CYP3A4 inhibitors: Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor. *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.	No change is made.
5. WARNINGS AND PRECAUTIONS **5.2 Hepatic Impairment** Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with TAXOTERE *[see Boxed Warning, Use in Specific Populations (8.6), Clinical studies (14)]*.	**5. WARNINGS AND PRECAUTIONS** **5.2 Hepatic Impairment** Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel *[see Boxed Warning, Use in Specific Populations (8.6), Clinical Studies (14)]*.	No change is made.
7. DRUG INTERACTIONS Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be	**7. DRUG INTERACTIONS** Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection Concentrate and drugs that inhibit CYP3A4 may increase exposure to	Throughout Section 7, TAXOTERE is changed by the Applicant to Docetaxel. The FDA reviewer has changed Docetaxel to the full product name Docetaxel Injection Concentrate.

avoided. In patients receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection Concentrate, close monitoring for toxicity and a Docetaxel Injection Concentrate dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.	
8. USE IN SPECIFIC POPULATIONS **8.4 Pediatric Use** Pharmacokinetics: Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2 . Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/ m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg h/mL. In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.	**8. USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** Pharmacokinetics: Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2 . Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg h/mL. In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.	No change is made.
8.6 Hepatic Impairment Patients with bilirubin >ULN should not receive TAXOTERE. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive TAXOTERE *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.	**8.6 Hepatic Impairment** Patients with bilirubin >ULN should not receive Docetaxel Injection Concentrate. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel Injection Concentrate *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.	Throughout Section 8.6, TAXOTERE is changed by the Applicant to Docetaxel. The FDA reviewer has changed Docetaxel to the full product name Docetaxel Injection Concentrate.
12. CLINICAL PHARMACOLOGY **12.3 Human Pharmacokinetics** Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase	**12. CLINICAL PHARMACOLOGY** **12.3 (b) (4) Pharmacokinetics** Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase	

1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^{2}to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel. Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/ m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.	1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel. Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*. Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug. Effect of Age: A population pharmacokinetic analysis was carried out after ~~Docetaxel~~ docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.	The FDA reviewer has changed Docetaxel to docetaxel in the place where the product was evaluated in the clinical trial by the innovator.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel. Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]* Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/ m^2 to 90 mg/ m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations. Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole *[see Dosage and Administration (2.7) and Drug-Drug Interactions (7)]*. Effect of Combination Therapies: • Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.	Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel. Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel Injection Concentrate. Patients with severe hepatic impairment have not been studied. *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]* Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations. Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole *[see Dosage and Administration (2.7)* and *Drug-Drug Interactions (7)]*. Effect of Combination Therapies: • Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.	The FDA reviewer has changed Docetaxel to the full product name Docetaxel Injection Concentrate.

• Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	• Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone. • Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug. • Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone. • Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.	

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

/s/

LILLIAN H ZHANG
01/13/2012

HONG ZHAO
01/13/2012
I concur.

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-356	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	April 29, 2011		
Division:	Division of Biologic Oncology Products	**Team Lead:** Angelica Dorantes, PhD	
Applicant:	Pfizer Inc.	**Acting Supervisor:** Angelica Dorantes, PhD	
Trade Name:	None proposed	**Date Assigned:**	May 11, 2011
Established Name:	Docetaxel	**Date of Review:**	December 23, 2011
Indication:	Breast Cancer; Non-Small Cell Lung Cancer; Prostate Cancer; Gastric Adenocarcinoma; Head and Neck Cancer	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Formulation/ strengths	Solution for Injection/ 10 mg/mL		
Route of Administration	IV injection		
Type of Review:	Biowaiver Request		

SUBMISSION:

This application is an electronic NDA, filed as a 505(b)(2) application, with Taxotere (NDA 20-449) as the RLD. The difference between the proposed product and the RLD is in the identity and amounts of the excipients and in the fact that the active pharmaceutical ingredient in the proposed drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. Reference is made to their IND 109,463 pre-IND/pre-NDA meeting held on November 11, 2010.

The proposed drug product is a sterile solution for IV injection containing docetaxel as the active ingredient. Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The proposed docetaxel injection (containing 10 mg docetaxel /mL) is a single use vial formulation (in volumes of 2, 8, 13, or 20 mL) that is ready for immediate dilution and administration (unlike the reference listed drug (RLD) that is a two vial product that requires a pre-mix step before dilution).

BIOPHARMACEUTIC INFORMATION:

The applicant is requesting a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(a) and (b)(1). The applicant claims that the bioequivalence of the proposed drug product and the RLD is supported by physicochemical data and non clinical studies as bioequivalence surrogate markers.

Assessment of Biowaiver Request

The composition for the formulation of the proposed Pfizer drug product and the RLD (Taxotere) drug product is as follows:

Name of ingredients	Taxotere	Pfizer Docetaxel Injection
Docetaxel	10mg/mL (when the two components have been reconstituted)	10mg/mL
Polysorbate-80	(b) (4) %v/v	(b) (4) %v/v
Propylene glycol	-	%v/v
Disodium edetate	-	0.01mg/mL
Ethanol	(b) (4) %v/v	40%v/v
Anhydrous citric acid	-	(b) (4) (b) (4) 3.5mg/mL)
Water for injections	(b) (4) %v/v	(b) (4)

Note that the active pharmaceutical ingredient in the proposed Pfizer drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. Both the proposed Pfizer Docetaxel Injection 10 mg/mL and Taxotere are diluted to a 0.74 mg/mL docetaxel (as anhydrous) admixture infusion solution, prior to use.

Comparison of the compositions of the RLD and proposed drug product admixtures (diluted infusion solutions):

Name of ingredients	Taxotere	Pfizer Docetaxel Injection
Docetaxel	0.74mg/mL	0.74mg/mL
Polysorbate-80	(b) (4) %v/v[1]	(b) (4) %v/v[2]
Propylene glycol	-	%v/v
Disodium edetate	-	g/mL
Ethanol	(b) (4) %v/v	%v/v
Anhydrous citric acid	-	ng/mL
Water for injections	(b) (4) %v/v	(b) (4)

Other Excipient(s): Include 0.9%w/v sodium chloride, or 5%w/v glucose, for both Taxotere and Pfizer Docetaxel Injection, depending on the choice of admixture diluent.

1 Equivalent to (b) (4)

2 Equivalent to

Both the proposed Pfizer's Docetaxel Injection and Taxotere are micelle-containing solutions, and the aqueous solubility of the active ingredient in both Pfizer's Docetaxel Injection and Taxotere is largely maintained by (b) (4) ((b) (4)) in a micelle system, when diluted as an admixture solution prior to intravenous use. The following comparative studies using the micellar admixtures prepared from the two products have been performed to demonstrate that the physical characteristics of the micelles and the solubility behaviors of the active ingredient in the solutions for intravenous use are comparable:

Test Attribute	Taxotere	Pfizer Docetaxel Injection
Critical micelle concentration (CMC)	(b) (4)	
Micelle size (and polydispersity) at (b) (4) at (b) (4)		
Accelerated physical stability ((b) (4)) at at		

Even thought the critical micelle concentrations of [redacted] (b) (4) in the admixtures are different, they both are at least [redacted] (b) (4) fold lower than the [redacted] (b) (4) concentration at the target admixture concentration, therefore, in both admixture solutions (prepared from the two drug products) micelles are formed and these micelles solubilize docetaxel in the dosing solution. The results indicate that the physical characteristics of the micelles and the solubility behavior of the active ingredient in the solutions for intravenous use are comparable. The applicant claims that owing to the similar docetaxel to [redacted] (b) (4) ratios in the two products, the physicochemical properties are similar, indicating that the bioavailability of Pfizer's Docetaxel Injection will be comparable to Taxotere.

Although not required, the applicant has performed a supportive non clinical bioequivalence study in dogs. According to the pharmacology/toxicology and the clinical pharmacology reviewers (Haw-Jyh Chiu, Ph.D. and Lillian Hua-Zhang, Ph.D.), the two drug products (Taxotere and the proposed Pfizer's docetaxel) are comparable in terms of their bioequivalence in dogs:

Species:	Dog (Beagle)	Dog (Beagle)
Gender/Number of Animals:	M/10[a]	M/10[a]
Feeding Condition:	Fasted[b]	Fasted[b]
Vehicle/Formulation:	Admixture of 0.74 mg/mL in saline	Admixture of 0.74 mg/mL in saline
Method of Administration:	IV infusion over 20 minutes	IV infusion over 20 minutes
Dose (mg/kg):	1	1
Sample:	Plasma	Plasma
Test Article:	Docetaxel Pfizer Injection	Taxotere®
Assay:	LC-MS/MS	LC-MS/MS
Parameters:		
C_{max} (ng/mL)	1420 (1200 – 1680)	1590 (1480 – 1700)
$AUC_{(0\text{-tlast})}$ (ng•h/mL)	507 (433 – 593)	576 (517 – 642)
Dose-normalized C_{max} (ng/mL / mg/kg)	1450 (1200 – 1740)	1500 (1400 – 1600)
Dose-normalized $AUC_{(0\text{-tlast})}$ (ng•h/mL / mg/kg)	516 (434 – 613)	543 (489 – 604)

In addition, no difference was observed between the two drug products (Taxotere and the proposed Pfizer's docetaxel) in the % docetaxel bound to plasma proteins in vitro using human and dog plasma:

Formulation	Matrix	Incubation Time (hours)	25°C % Bound	25°C SD	37°C % Bound	37°C SD
Taxotere (1 µg/mL)	Dog plasma	4	97.69	0.33	96.76	1.16
		6	97.03	1.29	96.07	0.31
		24	95.03	1.65	96.75	0.82
	Human plasma	4	98.06	0.32	97.60	0.10
		6	97.32	0.51	97.00	0.44
		24	94.91	0.44	96.64	0.04
Docetaxel Pfizer Injection (1 µg/mL)	Dog plasma	4	97.72	0.72	96.28	0.61
		6	96.62	0.51	95.10	1.30
		24	95.89	0.59	95.65	0.90
	Human plasma	4	97.84	0.21	97.18	0.87
		6	97.37	0.17	96.51	0.51
		24	95.95	0.46	96.70	0.63

Also, the rate and extend of docetaxel release from micellar saline solutions prepared using the two drug products was similar:

Study System: Micellar release of Pfizer Docetaxel Injection and Taxotere® at a concentration of [redacted] (b) (4) µg/mL in saline solution.

Test solution	Incubation Time (hours)	Dialysable Fraction [redacted] (b) (4)	% Micellar Release (SD) [redacted] (b) (4)
Docetaxel Pfizer injection	2		
	4		
	6		
	24		
Taxotere®	2		
	4		
	6		
	24		

It is further noted that in addition to the one vial docetaxel drug products approved under NDA 20-449/supplement S-054 (Taxorere from Sanofi), several other docetaxel one vial drug products have recently been approved as original NDA/505(b)(2) applications (NDA 22-234 from Hospira and NDA 201-525 from Sandoz), with the following formulations:

Ingredients	TAXOTERE Docetaxel Inj \ 20mg/1 ml	TAXOTERE Docetaxel Inj \ 80 mg/4 ml	HOSPIRA Docetaxel Inj (b) (4)	SANDOZ Docetaxel Inj 20mg/2 ml	SANDOZ Docetaxel Inj 80mg/8 ml
Docetaxel	20 mg	80 mg	10 mg	20 mg	80 mg
Polysorbate 80	0.54 g (50% v/v)	(b) (4) g (50% v/v)	260 mg	160 mg	640 mg
Ethanol anhydrous	(b) (4)	(b) (4)	(b) (4)	551.8 mg	2207.2 mg
Volume of Diluent	0.395 g (50% v/v)	1.58 g (50% v/v)	(D) (4)	(b) (4)	
Citric Acid	-	-	4 mg	8 mg	32 mg
PEG 300	-	-	(b) (4)	1,296 mg	5,184 mg
(b) (4)			(D) (4)		
(D) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Additionally, this review is referencing the Citizen Petition by Sanofi-Aventis (dated 6/12/2009), claiming that approval of drug products having formulations with a different polysorbate 80 to docetaxel ratio than their original Taxotere formulation should require clinical data to demonstrate that the unbound docetaxel concentration is not changed compared to Taxotere. Dr. Julie Bullock, Clinical Pharmacology TL, from OCP addressed some of the Citizen Petition issues and according to the her review of this Citizen Petition dated 12/14/2009, changes to the concentration of polysorbate 80 do not have a significant impact on the pharmacokinetics of docetaxel. That review also notes that OCP does not agree with the petitioner's assertion that levels of unbound docetaxel are more significant (to assure safety and effectiveness) than total docetaxel levels.

According to 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 of 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 has the same dosage form, route of administration and indication as the RLD. 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 (ethanol and propylene glycol) are not expected to impact the amount of drug delivered to the site of action, based on comparable physical characteristics of the micelles and the solubility behavior of the active ingredient in the solutions for intravenous use. Based on the overall provided data and previous data knowledge, it is concluded that the bioavailability of Pfizer Docetaxel Injection 10 mg/mL 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.

RECOMMENDATION:
A waiver of the *in vivo* bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 202-356 for Docetaxel Solution for Injection ([(b) (4)]/mL) is recommended for approval.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
12/23/2011

ANGELICA DORANTES
12/23/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Information			
NDA/BLA Number	202-356	**Brand Name**	Docetaxel Injection Concentrate
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Docetaxel
Medical Division	OND/OODP/DBOP	**Drug Class**	A microtubule inhibitor belonging to the taxoid family
OCP Reviewer	Lillian Hua Zhang, Ph D	**Indication(s)**	As an antineoplastic agent for the treatment of • Breast cancer (BC) • Non-small cell lung cancer (NSCLC) • Hormone refractory prostate cancer (HRPC) • Gastric adenocarcinoma (GC) • Squamous cell carcinoma of the head and neck cancer (SCCHN)
OCP Team Leader	Hong Zhao, Ph D	**Dosage Form**	An intravenous (IV) solution containing 10 mg/mL of docetaxel in single-use vials (20 mg/2 mL; 80 mg/8 mL; 130 mg/13 mL; and 200 mg/20 mL)
Pharmacometrics Reviewer	N/A	**Dosing Regimen**	Administer intravenously over 1 hour every 3 weeks • BC locally advanced or metastatic: 60 mg/m^2 to 100 mg/m^2 single agent • BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles • NSCLC after platinum therapy failure: 75 mg/m^2 single agent • NSCLC chemotherapy-naive: 75 mg/m^2 followed by cisplatin 75 mg/m^2 • HRPC: 75 mg/m^2 with 5 mg prednisone twice a day continuously • GC: 75 mg/m^2 followed by cisplatin 75 mg/m^2 followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion • SCCHN: 75 mg/m^2 followed by cisplatin 75 mg/m^2 IV (day 1), followed by fluorouracil 750 mg/m^2 per day as a 24-hr IV (days 1–5), starting at end of cisplatin infusion; for 4 cycles or 75 mg/m^2 followed by cisplatin 100 mg/m^2 IV (day 1), followed by fluorouracil 1000 mg/m^2 per day as a 24-hr IV (days 1–4); for 3 cycles
Date of Submission	29-April-2011	**Route of Administration**	IV
Estimated Due Date of OCP Review	21-December-2011	**Sponsor**	Pfizer
Medical Division Due Date	21-January-2012	**Priority Classification**	Standard
PDUFA Due Date	29-February-2012		

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Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References				
Total Number of Studies				

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Comments:
This is a 505(b)(2) application submitted by Pfizer using Taxotere® approved by FDA under NDA 20-449 (Sanofi Aventis) as the reference listing drug (RLD).

Docetaxel Injection Concentrate (containing 10 mg/mL of docetaxel) developed by Pfizer is a solution formulation in single use vials that does not require a pre-mix step (dilution with a diluent) as the RLD and is ready for further dilution for intravenous (IV) administration. The RLD product is a solution formulation (40 mg/mL) that requires reconstituted with sterile WFI, USP, as the first pre-mix step prior to further dilution for IV administration. Pfizer's Docetaxel Injection has the same dosage form and route of administration as the RLD. After the pre-mix step for the RLD, the dose strength of the active ingredient is also the same for the two products. The difference between the two products is the composition of the inactive ingredients. A comparison of the formulation of Pfizer Docetaxel Injection 10 mg/mL with Taxotere ("pre-mix" solution) is presented in the table below:

Name of ingredients	Taxotere	Pfizer Docetaxel Injection
Docetaxel	10mg/mL (when the two components have been reconstituted)	10mg/mL
Polysorbate-80	(b) (4) %v/v	(b) (4) %v/v
Propylene glycol	-	%v/v
Disodium edetate	-	0.01mg/mL
Ethanol	(b) (4) %v/v	40%v/v
Anhydrous citric acid	-	(b) (4) (b) (4) 3.5mg/mL)
Water for injections	(b) (4) %v/v	(b) (4)

Pfizer has requested a waiver of an *in vivo* bioequivalence (BE) study and has conducted an animal study to compare the pharmacokinetics of Pfizer Docetaxel Injection Concentrate, 10 mg/mL, to Taxotere after a single IV infusion in male Beagle dogs. The biopharmaceutics review by the Office of New Drug Quality Assessment concludes that the sponsor's biowaiver request appears reasonable, but the final decision on the waiver will be made during the review of this NDA.

The requested pediatric study waiver will be discussed at the PeRC meeting scheduled on June 29, 2011.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?		x		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes___

If the NDA/BLA is not fileable from the clinical pharmacology 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.
None

Lillian Hua Zhang, Ph.D.	07-June-11
Reviewing Clinical Pharmacologist	Date
Hong Zhao, Ph.D.	07-June-11
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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/s/

LILLIAN H ZHANG
06/07/2011

HONG ZHAO
06/07/2011
I concur.

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-356	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	April 29, 2011		
Division:	Division of Biologic Oncology Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Pfizer Inc.	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	Docetaxel Injection	**Date Assigned:**	May 11, 2011
Established Name:	Docetaxel	**Date of Review:**	June 7, 2011
Indication:	Breast Cancer; Non-Small Cell Lung Cancer; Prostate Cancer; Gastric Adenocarcinoma; Head and Neck Cancer	**Type of Submission:** Original New Drug Application – 505(b)(2)	
Formulation/ strengths	Solution for injection/ 10 mg/mL		
Route of Administration	IV injection		

SUBMISSION:

The proposed drug product is a sterile solution for IV injection containing docetaxel as the active ingredient. Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The proposed docetaxel injection (containing 10 mg docetaxel /mL) is a single use vial formulation (2, 8, 13, or 20 mL) that is ready for immediate dilution and administration (unlike the reference listed drug (RLD) that is a two vial product that requires a pre-mix step before dilution). This application is an electronic NDA, filed as a 505(b)(2) application, with Taxotere as the RLD. The difference between the proposed product and the RLD is in the identity and amounts of the excipients and the active pharmaceutical ingredient in the proposed drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. Reference is made to the IND 109463 pre-IND/pre-NDA meeting held on November 11, 2010.

BIOPHARMACEUTIC INFORMATION:

The applicant requests a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1)(i) and (ii). The applicant claims that the bioequivalence of the proposed drug product and the RLD is supported by physicochemical data and non clinical studies as bioequivalence surrogate markers.

The composition of the RLD and the proposed drug product is as follows:

Name of ingredients	Taxotere	Pfizer Docetaxel Injection
Docetaxel	10mg/mL (when the two components have been reconstituted)	10mg/mL
Polysorbate-80	(b) (4) %v/v	(b) (4) %v/v
Propylene glycol	-	%v/v
Disodium edetate	-	0.01mg/mL
Ethanol	(b) (4) %v/v	40%v/v
Anhydrous citric acid	-	(b) (4) (b) (4) 3.5mg/mL)
Water for injections	(b) (4) %v/v	(b) (4)

Note that the active pharmaceutical ingredient in the proposed Pfizer drug product is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. Both the proposed Pfizer Docetaxel Injection 10 mg/mL and Taxotere are diluted to a 0.74 mg/mL docetaxel (as anhydrous) admixture infusion solution, prior to use.

Comparison of the RLD and proposed drug product admixtures (diluted infusion solutions):

Name of ingredients	Taxotere	Pfizer Docetaxel Injection
Docetaxel	0.74mg/mL	0.74mg/mL
Polysorbate-80	(b) (4) %v/v[1]	(b) (4) %v/v[2]
Propylene glycol	-	%v/v
Disodium edetate	-	g/mL
Ethanol	%v/v	%v/v
Anhydrous citric acid	-	ng/mL
Water for injections	%v/v	(b) (4)

Other Excipient(s): Include 0.9%w/v sodium chloride, or 5%w/v glucose, for both Taxotere and Pfizer Docetaxel Injection, depending on the choice of admixture diluent.

1 Equivalent to (b) (4)

2 Equivalent to

Both Pfizer's Docetaxel Injection and Taxotere are micelle-containing solutions, and the aqueous solubility of the active ingredient in both Pfizer's Docetaxel Injection and Taxotere is largely maintained by (b) (4) in a micelle system, when diluted as an admixture solution prior to intravenous use. A series of comparative studies have been performed to demonstrate that the physical characteristics of the micelles and the solubility behaviors of the active ingredient in the solutions for intravenous use are comparable, owing to the similar docetaxel to (b) (4) ratios in the two products. The applicant claims that the physicochemical data indicate that the bioavailability of Pfizer's Docetaxel Injection will be comparable to Taxotere. Reference is made to the Section 2.4 (Non Clinical Overview) for further discussion on other relevant, non clinical studies undertaken by the applicant as bioequivalence surrogate markers, to support an exemption from performing bioequivalence studies. Reference to also made to Section 2.5 (Clinical Overview) for further discussion on the pharmacokinetics of Pfizer's Docetaxel Injection and Taxotere.

The review of this submission will consist on the evaluation of the overall information supporting the biowaiver request. Please note that if during the review cycle the other reviewing disciplines (i.e., clinical and pharmacology/toxicology, etc.) do not have any safety concerns regarding the excipients and the percentage of these excipients in the proposed injection, the biowaiver for the proposed Docetaxel Injection product may be granted.

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 202-356 for filing purposes. The sponsor has submitted a reviewable submission. There are no comments to be conveyed to the sponsor at this time.

NDA 202-356 is filable from a Biopharmaceutics perspective.

Signature	**Signature**
Biopharmaceutics Reviewer Office of New Drugs Quality Assessment	Biopharmaceutics Team Leader or Supervisor Office of New Drugs Quality Assessment

cc:

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/s/

ELSBETH G CHIKHALE
06/07/2011

ANGELICA DORANTES
06/07/2011