CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review (2)

Date	March 10, 2014
From	Ali Al-Hakim, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202356
Applicant	Pfizer, Inc.
Date of Original Submission **Date of Resubmission**	August 14, 2012 September 13. 2013
PDUFA Goal Date	March 13, 2014
Proprietary Name / **Established Name**	N/A Doxcetaxel
Dosage forms / Strength	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Head and neck cancer
Recommended	Approval

1. Introduction

NDA 202356 **(Doxcetaxel)** was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to the Agency on August 30, 2011. This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends an Approval action for this application. All individual discipline reviews may be found in DARRTS.

The original CTDL recommendation for the NDA was a Complete Response (CR) action as indicated in CTDL review conducted by Dr. Nallaperum Chidambaram and dated January 31, 2013.

A complete response letter was issued on February 29, 2013. The applicant responded to the complete response letter on September 13, 2013.

Therefore, this CTDL(review no. 2) will focus only on addressing the responses to the CR Action issues and will reference any other unchanged information to the original CTDL(review No. 2). The main issue delineated in the first CTDL includes topics related to CMC, safety and cGMP inspection.

2. Background

The Reference Listed Drug for this submission is the one-vial formulation of Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), which is currently marketed by Sanofi Aventis. Taxotere® was approved on August 02, 2010 with one-vial formulation with a concentration of 20 mg/mL

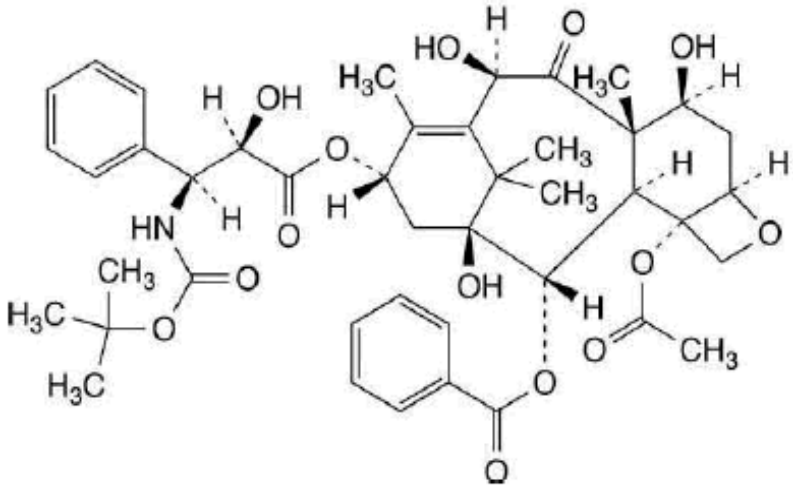
The proposed drug product for the current NDA is a "ready to use" product containing the drug substance (in solution) in one vial. However, in this NDA, the solution is intended for reconstitution and subsequent intravenous injection. Docetaxel Injection is supplied in four presentations (20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL). All four presentations utilize the same concentration of 10 mg/mL. The proposed drug product is formulated with polysorbate 80 as a (b) (4), propylene glycol and ethanol as (b) (4), disodium edentate as a (b) (4), and citric acid for pH adjustment.

Dosing Regimen and Administration

The drug product is to be used for once every 3 weeks dosing as an intravenous infusion administered over one hour at a dose of 60-100 mg/m^2. Refer to the Medical Officer's 11-JAN-2013 review for additional details.

3. Chemistry, Manufacturing and Control (CMC)

Drug Substance



Chemical Name:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2(b)(4)-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate
Empirical formula: $C_{43}H_{53}NO_{14}$
Molecular weight: 807 (b) (4)

Docetaxel is an anhydrous, white to almost-white powder that is freely soluble in polar organic solvents such as ethanol and is insoluble in water. Its physicochemical properties related to chirality, solubility, polymorphism, and hygroscopicity may

influence drug product performance and manufacturability. A major [redacted] impurity ([redacted]) is formed by [redacted]. X-ray diffraction has identified [redacted] morphic forms that are created when different solvents are used. The desired morphic form ([redacted] is produced during manufacture via [redacted].
Due to its highly hygroscopic nature and the effect of water on the drug substance, it was packaged in [redacted] ([redacted]) bags, in [redacted] bottle with [redacted]. The drug substance is sourced from [redacted] (DMF [redacted]).

Drug Product
Docetaxel Injection is a clear, colorless to brown-yellow solution formulated as a sterile nonaqueous solution intended for dilution into an infusion solution (isotonic normal saline). The proposed undiluted Docetaxel Injection formulation contains docetaxel (anhydrous) as the active ingredient. The proposed drug product is formulated with polysorbate 80 as a [redacted], propylene glycol and ethanol as [redacted], disodium edentate as [redacted], and citric acid as pH adjustment. Docetaxel Injection 10 mg/mL is presented as a single strength 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). All four presentations are packaged in 2 mL, [redacted], and 20 mL polypropylene vials closed with [redacted] ([redacted]) rubber stoppers and over sealed with [redacted] crimps and [redacted] flip-off seals. The vials are packaged in cartons.

CMC review
The CMC reviewer, Dr. Josephine Jee, reported in her review # 4 dated January 24, 2014 that the CMC outstanding issues listed below were adequately addressed by the sponsor and that the NDA is recommended for approval from CMC point of view.

- Providing actual representative components and compositions (per vial, not per mL) for each of the four proposed presentations and Listing of the exact amount of propylene glycol and polysorbate-80 for the formulation per vial
- Revising the acceptance criteria for ethanol content to be [redacted]% of the actual amount added in the components and composition statement (e.g., 40%v/v would be [redacted]%v/v).
- Including the test for alcohol content in the Post-Approval Stability Protocol and Stability Commitment and provide the stability data obtained for ethanol content.
- Providing compatibility data for your drug product generated using the proposed infusion line (e.g., polyethylene-lined administration) under the conditions described in the proposed package insert.

Additional CMC related issues related to alcohol content.
The CMC reviewer reported that the proposed amount of ethanol in the proposed Docetaxel Injection is higher than the RLD and all other related approved drug products. The high content of alcohol content in the drug product formulation has raised many concerns among various disciplines during NDA team meetings. For details discussion regarding this issue, see updated discussion and recent reviews comments below in items 8 (safety) and (Office of Surveillance and Epidemiology).

Expiry Dating:
Based on the stability data provided, a 24-month expiration dating period is granted for the drug product when stored under the proposed storage conditions (between 2°C to 25°C).
The NDA is recommended for approval from CMC perspective.

ONDQA Biopharm review
The Biopharm reviewer (Dr. Elsbeth Chikhale) noted in her review dated November, 19, 2012 that the CR letter dated February 29, 2012 did not include Biopharmaceutics deficiencies and that there is no change to the drug product formulation to that was submitted in the original submission, therefore the request to waive the *in vivo* bioequivalence study requirement remains acceptable and that this application is recommended for approval.

Microbiology
The Microbiology reviewer (Dr. J. Metcalfe) reported in his review dated January 31, 2013 that the resubmission did not contain any new product Microbiology issues to be reviewed.

cGMP facilities inspection/ Establishment Evaluation Request (EER)
An Establishment Evaluation Request (EER) was submitted to the Office of Compliance and an overall acceptable recommendation for all facilities was issued for the application on December 13, 2013.

4. Nonclinical Pharmacology/Toxicology

The non clinical Pharmacology/Toxicology Reviewer, Dr. Haw-Jyh Chiu, recommended approval for this NDA (review dated February 24, 2014). Dr. Chiu reported that there were no nonclinical issues identified in the Complete Response Letter and Pfizer did not submit any new nonclinical data in this resubmission.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Jeanne Fourie Zirkelbach) reported in her review dated January 24, 2014 that A FDA Complete Response (CR) Letter was issued on February 14, 2013 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 December 23, 2011). 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.

6. Clinical Microbiology

Not Applicable

7. Clinical/ Statistical Efficacy

No new clinical data were provided for this submission.

8. Safety

The clinical reviewer, Dr. William Pearce, concluded in his review dated February 26, 2014 that the total ethanol (ETOH) dose and estimated blood ETOH concentrations were higher for Pfizer docetaxel (15 mg/dL) than for the referenced drug product (Taxotere 2-vial formulation) (5 mg/dL) or for the currently marketed Taxotere 1-vial formulation (~10 mg/dL). For the low-moderate levels of ETOH exposure delivered by these docetaxel products, the small increase in the ETOH exposure for Pfizer docetaxel is not expected to result in significant differences in psychomotor dysfunction, CNS depression, or the overall safety profile when compared to other approved docetaxel products.

The total doses of propylene glycol (PG) appear to be below the threshold of clinical relevance. PG is not expected to produce alcohol intoxication at the recommended dose or schedule that Pfizer docetaxel is administered. Pharmacokinetic interactions resulting in further elevations in blood ETOH or PG concentrations are not predicted to significantly increase the exposure of ETOH or PG for Pfizer docetaxel. The additive effects of PG to ETOH-related CNS depression or behavioral effects are expected to be minimal at these exposure levels.

Since it is desirable to minimize the ETOH exposure in vulnerable or sensitive patients as much as possible, labeling that includes a contextual statement with ETOH dose level for each docetaxel product is expected to adequately manage the small differences in alcohol exposure. The labeling content incorporated into the Pfizer docetaxel prescribing information (USPI) and patient package insert (PPI) is

expected to adequately manage potential safety risks associated with alcohol exposure. The other approved docetaxel product USPI and PPIs should be updated with labeling content consistent with the alcohol content-related labeling in the Pfizer docetaxel USPI and PPI. This will enable adequate assessments of the ethanol content across these products by healthcare practitioners and facilitate appropriate management of alcohol related risks in sensitive or vulnerable patient populations. Dr. Pearce also reported that "cases of alcohol intoxication have been reported for the currently marketed docetaxel formulations. Pfizer docetaxel has more alcohol than all of the currently marketed docetaxel products at the present time, so these cases are relevant, and warrant labeling statements in the Pfizer docetaxel USPI."

9. Office of Surveillance and Epidemiology (DPV)

DOP1 has consulted the Division of Pharmacovigilance II (DPV II) to review the FDA Adverse Event Reporting System (FAERS) and the literature for an association between treatment with parenteral docetaxel regarding ethanol content and symptoms of alcohol intoxication.

DPV reported in a memo dated 02/13/2014 that the proposed Pfizer docetaxel product labeling with warnings for alcohol intoxication generally acceptable. We recommend adding language to convey the potential additive effects of propylene glycol and alcohol. Also, it may be helpful to add a time frame, such as "immediately after infusion" to the statement cautioning against operating machinery or driving. Finally, for the purposes of patient education and practitioner monitoring during drug administration, we recommend that all docetaxel formulations be uniformly labeled regarding the risks of alcohol intoxication. Based on the above information and related concerns from safety reviewer, DPV and other disciplines with respect to high alcohol content, the following statement regarding alcohol content was added to the label (PI).

Cases of alcohol intoxication have been reported with docetaxel, including other formulations of docetaxel. The alcohol content in a dose of Docetaxel Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Docetaxel Injection on the ability to drive or use machines immediately after the infusion. Each administration of Docetaxel Injection at 100 mg/m^2 delivers 3.2 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 6.4 grams of ethanol *[see Description (11)]*. Other docetaxel products may have a lesser amount of alcohol.

10. Postmarket Experience

Not Applicable

11. Advisory Committee Meeting

This product was not discussed at an Advisory Committee meeting.

12. Pediatrics

Not Applicable

13. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.
- Exclusivity or patent issues of concern: No issues were noted for this NDA.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None

14. Labeling

Division of Medication Error Prevention and Analysis (DMEPA), Dr. JIBRIL ABDUS-SAMAD, reported in his review dated March 07, 2013 that the sponsor agreed to the following changes:

- Delete the word *Concentrate* from the established name in the prescribing information
- Replace the abbreviation *IV* with the words *intravenously* or *intravenous infusion*
- Revise the formatting to place the concentration of the final solution (0.3 mg/mL to 0.74 mg/mL) to appear on the same line.

Dr. ABDUS-SAMAD concluded that the Applicant has addressed DMEPA's concerns with the prescribing information.

Division of Medical Policy Programs (DMPP) concluded in a review dated March 04, 2014 that the PPI is acceptable with the recommended changes which include items related to simplified wording and clarified concepts where possible and ensuring that the PPI is consistent with the Prescribing Information (PI)

Proprietary name:
There was no proprietary name proposed for this product.

15. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

- Risk Benefit Assessment
  The review of this NDA is based primarily on chemistry, manufacturing and controls data.

- Recommendation for Postmarketing Risk Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant
  None

Overall Conclusion
The NDA is recommended for approval.

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Office of New Drug Quality Assessment
OPS-CDER

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/s/

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03/11/2014