CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	3/12/2014
From	Amna Ibrahim MD
Subject	Division Director Summary Review
NDA #	202356
Applicant Name	Pfizer Labs
Date of Submission	09/13/2013
PDUFA Goal Date	03/13/2014
Established (USAN) Name	Docetaxel Injection
Dosage Forms / Strength	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL
Proposed Indication(s)	1. For the treatment of patients with locally advanced or metastatic **breast cancer** after failure of prior chemotherapy. 2. In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive **breast cancer**. 3. As a single agent for the treatment of patients with locally advanced or metastatic **non-small cell lung cancer** after failure of prior platinum-based chemotherapy. 4. In combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic **non-small cell lung cancer** who have not previously received chemotherapy for this condition. 5. In combination with prednisone the treatment of patients with androgen independent (hormone refractory) metastatic **prostate cancer**. 6. In combination with cisplatin and fluorouracil for the treatment of patients with advanced **gastric adenocarcinoma**, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. 7. In combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced **squamous cell carcinoma of the head and neck** (SCCHN).
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Pierce/Maher
Statistical Review	NA
Pharmacology Toxicology Review	Chiu/Palmby
CMC Review/OBP Review	Jee/Al Hakim
Microbiology Review	Metcalfe
Clinical Pharmacology Review	Zirklebach/Liu
DDMAC	Toscano
DSI	NA
CDTL Review	Al Hakim
OSE/DMEPA	Abdus Samad
OSE/DPV II	Rand
OSE/DMPP	Caulk

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

NDA 202356 for Docetaxel injection Concentrate was originally submitted on April 29, 2011 for approval under Section 505(b)(2) as an alternative formulation to the reference listed drug (RLD) Taxotere. After a standard review, a Complete Response letter was issued on February 29, 2012 due to multiple CMC deficiencies including an incomplete DMF. A Class 2 submission was received on August 14, 2012. Due to clinical concerns about safety and CMC deficiencies, a Complete Response action was taken. Finally, the 505b2 NDA has been submitted for the 3rd cycle, addressing the deficiencies of the previous submissions.

2. Background

The applicant has re-formulated docetaxel in a single vial formulation and avoids pre-mixing. It is ready for immediate dilution and administration. However, ethanol and propylene glycol have been added as excipients in amounts greater than the RLD or any other docetaxel formulations as identified by the applicant. This division was concerned that the greater amount of ethanol in this formulation may cause increased side effects from this product. In addition, the toxicity may be increased due to pharmacokinetic interaction between ethanol and propylene glycol.

For the 2nd cycle CR, the CMC deficiencies related to components/composition statement to the amount of ethanol, propylene glycol and polysorbate-80; acceptance criteria for ethanol; testing for ethanol on stability; and in-use stability data. In addition, the potential toxicity profile in patients from ethanol and propylene glycol in the amounts in the formulation was not addressed adequately in the NDA by the applicant.

3. CMC/Device

Per Josephine Jee PhD, "NDA 202356 is recommended for approval from Chemistry, Manufacturing, and Control perspective. 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)."

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

According to Haw-Jyh Chiu PhD, "(t)he nonclinical discipline recommended NDA 202356 for Docetaxel Injection for approval following review of nonclinical data provided in the previous resubmission. From the nonclinical perspective, since no new nonclinical data were provided and the overall nonclinical information in NDA 202356 has not changed, this resubmission of NDA 202356 for Docetaxel Injection is recommended for approval for the proposed indications."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Per Jeanne Fourie Zirkelbach PhD, "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)." She also stated that "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 alcoholdehydrogenase (ADH), pharmacokinetic drug interactions resulting in further elevations in blood ethanol or propylene concentrations are not likely."

I concur that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

No new information was submitted for clinical microbiology

7. Clinical/Statistical-Efficacy

No new data was submitted for efficacy.

8. Safety

Primary reviewer William Pierce stated, "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 (see Section 8 of this review). 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."

Division of Pharmacovigilance II (DPV II) was consulted to review the FDA Adverse Event Reporting System (FAERS) and the literature for an association between treatment with parenteral docetaxel (containing ethanol) and symptoms of alcohol intoxication. Margaret Rand, PharmD, BCOP, states "We identified three cases consistent with alcohol intoxication associated with docetaxel in FAERS. They are all foreign reports involving at least two different formulations of docetaxel. There is a strong temporal association between the docetaxel infusion and symptoms of alcohol intoxication in these cases (two occurred during the infusion and one within 24 hours of drug administration). The symptoms of alcohol intoxication were listed as "transient" in one case and in another case the symptoms resolved in time for the patient to finish his treatment using a slower infusion rate. In two of the three cases, the reporters planned to use a different docetaxel formulation with lower alcohol content for future treatments." She concludes that there are postmarketing cases of alcohol intoxication associated with docetaxel and literature to support this potential adverse event. Four currently approved drugs (IV ethanol, Sandimmune, Taxol, and Kaletra) which contain alcohol can serve as a guide for labeling Pfizer's docetaxel formulation. Lastly, regardless of the amount of alcohol in the various docetaxel formulations, the product labels should be standardized to warn practitioners and patients of the risk of alcohol intoxication. She recommends adding language in the label to convey the potential additive effects of propylene glycol and alcohol. She also states that 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, DPVII recommends that all docetaxel formulations be uniformly labeled regarding the risks of alcohol intoxication.

9. Advisory Committee Meeting

None

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

- DSI Audits: No clinical data was submitted and no DSI audit was performed.
- Other consult: Marybeth Toscano from DDMAC had no comments in her review of the PI. Jibril Abdus-Samad PharmD states in his review that all of DMEPAs comments were adequately addressed.

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name: N/A
- Physician labeling: all major issues were resolved.
- Carton and immediate container labels: all major issues were resolved.
- Patient labeling/Medication guide: all major issues were resolved.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approved

- Risk Benefit Assessment

  This 505B2 application relies on the listed drug for demonstration of efficacy and efficacy. There may a slightly increased risk of alcohol intoxication due to the ethanol content as excipient. However, this risk is considered quite low and is addressed by adding a section in the Warning and Precautions section in the label.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  None

  Amna Ibrahim MD
  Deputy Director
  DOP1, OHOP, CDER

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/s/

AMNA IBRAHIM
03/12/2014

Summary Review for Regulatory Action

Date	February 14, 2013
From	Amna Ibrahim MD
Subject	Deputy Director Summary Review
NDA #	202356 Class 2 resubmission
Applicant Name	Pfizer Labs
Date of Submission	08/14/2012
PDUFA Goal Date	02/14/2013
Established (USAN) Name	Docetaxel Injection Concentrate
Dosage Forms / Strength	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL and 200 mg/20 mL 10 mg/mL
Proposed Indication(s)	1. For the treatment of patients with locally advanced or metastatic **breast cancer** after failure of prior chemotherapy. 2. In combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive **breast cancer**. 3. As a single agent is indicated for the treatment of patients with locally advanced or metastatic **non-small cell lung cancer** after failure of prior platinum-based chemotherapy. 4. In combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic **non-small cell lung cancer** who have not previously received chemotherapy for this condition. 5. In combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic **prostate cancer**. 6. In combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced **gastric adenocarcinoma**, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. 7. In combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced **squamous cell carcinoma of the head and neck** (SCCHN).
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	William Pierce
Pharmacology Toxicology Review	Haw-Jay Chiu
CMC Review	Josephine Jee
Microbiology Review	Steven Fong
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach
CDTL Review	Nallaperumal Chidambaram
OSE/DMEPA	James Schlick

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

1. Introduction

NDA 202356 for Docetaxel injection concentrate was originally submitted on April 29, 2011 for approval under Section 505(b)(2) as an alternative formulation to the reference listed drug (RLD) Taxotere. After a standard review, a Complete Response letter was issued on February 29, 2012 due to multiple CMC deficiencies including an incomplete DMF.

A Class 2 submission was received on August 14, 2012. Due to clinical concerns about safety and CMC deficiencies, a Complete Response action will be taken.

2. Background

The applicant has re-formulated docetaxel in a single vial formulation and avoiding pre-mixing. It is ready for immediate dilution and administration. However, ethanol and propylene glycol have been added as excipients in amounts greater than the RLD or any other docetaxel formulations as identified by the applicant. It is not known whether

3. CMC/Device

Josephine Jee, CMC reviewer, recommends a Complete Response from CMC perspective. Sponsor was not able to respond completely to some comments previously communicated. In addition, new deficiencies have been identified. As summarized by CDTL Nallaperum Chidambaram, PhD, the CMC deficiencies relate to components/composition statement to indicate the exact amount of ethanol, propylene glycol and polysorbate-80; acceptance criteria for ethanol; testing for ethanol on stability; and in-use stability data.

In an email dated February 8, 2013, and per memo dated 2/11/2013 by Josephine Jee, an overall acceptable Compliance recommendation has been provided.

I concur with the conclusions reached by the chemistry reviewer regarding the recommendation for a Complete Response from the CMC perspective. Manufacturing site inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

Haw-Jyh Chiu, Ph.D, toxicology reviewer, states that in this resubmission, Pfizer addressed two nonclinical-related deficiencies contained in the Completed Response Letter for the original NDA submission. These comments were in regards to impurity specification and leachable levels for Docetaxel Injection Concentrate. He states that from the perspective of the nonclinical discipline, the proposed impurity specification and justification for the levels of leachables in Docetaxel Injection Concentrate are acceptable for the proposed indications. Dr Haw-Jyh's review was cosigned by his Team Leader Todd Palmby PhD.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

In her review, Jeanne Fourie Zirkelbach, PhD states that the response to the Compete Response Letter did not contain any new Clinical Pharmacology data. She states that "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." Qi Liu, PhD., her Team Leader has co-signed the review.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Steven Fong PhD and John Metcalfe PhD recommended approval from a microbiology quality standpoint for the initial submission in their review dated 1/25/2012.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This NDA relies on the efficacy findings of the RLD, Taxotere. No efficacy data was submitted for this NDA.

8. Safety

No new clinical studies were conducted to support this NDA. Instead, this NDA relies upon the efficacy and safety findings of the RLD Taxotere. The RLD or the other single vial formulations of docetaxel referenced by the applicant have less ethanol and no propylene glycol. The potential toxicity

profile in patients from ethanol and propylene glycol in the amounts in the formulation has not been addressed adequately in the NDA by the applicant.

In the proposed labeling, the applicant included new Warning and Precautions in the labeling, based on the alcohol content. The applicant as an explanation for the addition of new Warning and Precautions sections in the label stated that "Pfizer's formulation contains propylene glycol and higher levels of ethanol, both of which can contribute to alcohol-like symptoms." The applicant was queried about the risks from the alcohol and propylene glycol; however a satisfactory explanation was not provided. Furthermore, according to the applicant, the total "daily intake of ethanol" from the Pfizer docetaxel would be 6.4 g assuming a dose of 200 mg. The applicant has referred to a European Guidance document in their submission titled "*Excipients in the label and package leaflet of medicinal products for human use*". This document provides a list of the excipients which should be included in the labeling and outlines the information which should appear in the package leaflet for these excipients. According to this Guidance, warning statements are required in labels for ethanol levels of over 100 mg. The applicant also argued that paclitaxel and phenytoin may have a higher amount of ethanol or propylene glycol; however this is not relevant to the Pfizer docetaxel formulation that is relying on the safety findings of the RLD.

William Pierce, PharmD, states in the clinical review that "the ethanol and propylene glycol in the proposed Pfizer docetaxel formulation may result in a difference in the safety profiles between Pfizer docetaxel and the referenced drug (Taxotere). A 505(b)(2) NDA application requires full reports of investigations of safety (and effectiveness) are provided to determine if the proposed product can rely on the safety (and efficacy) findings from the referenced product (i.e., Taxotere). For this 505(b)(2) NDA, the Applicant proposed unique Warnings and Precautions related to potential alcohol-related toxicities in the Pfizer docetaxel labeling, despite the absence of this information in all of the previously approved docetaxel products currently marketed in the US; all of which result in lower ethanol and propylene glycol (none) exposures per dose. The labeling for 505(b)(2) submissions are not required to be identical to the referenced listed drug product. However, the proposal to add a unique Warning and Precaution to labeling by the Applicant, as in this case, is highly suggestive of a significant difference in the clinical safety of the proposed Pfizer docetaxel and the referenced product Taxotere. This is problematic since the premise of this (b)(2) NDA relies solely on the clinical findings for safety from the referenced drug, Taxotere."

"The magnitude of the potential effect and the difference between this docetaxel product and the referenced drug remains uncertain without additional clinical information. Based on the European Guidance, the Pfizer docetaxel product will likely result in clinically relevant blood alcohol levels. Compared to Taxotere, Pfizer docetaxel delivers a two- to three- fold increase in the amount of ethanol per dose. This increases to approximately four-fold per dose when theoretically factoring in the additive effect of propylene glycol. The magnitude and/or the duration of the alcohol-related toxicities may be further increased due to a potential interaction between ethanol and propylene glycol via the primary metabolic elimination pathway, alcohol dehydrogenase, for both substances."

The clinical reviewers state "Based on this unresolved safety issue, which appears to be unique to Pfizer docetaxel, the Clinical Reviewer recommends that this 505(b)(2) resubmission receive a Complete Response."

9. Advisory Committee Meeting

None

10. Pediatrics

Not applicable

11. Other Relevant Regulatory Issues

- DSI Audits: none
- Financial Disclosure: NA
- Other consults: none

There are no other unresolved relevant regulatory issues.

12. Labeling

Not discussed due to CR action.

- Proprietary name: N/A
- Physician labeling: Not discussed because of the CR action
- Carton and immediate container labels: Comments were provided James Schlick, RPh, MBA, but labeling discussions have not taken place with the applicant.
- Patient labeling/Medication guide: DMPP deferred comments because of the planned CR action.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  This NDA can not be approved due to deficiencies as noted. A Complete Response action will be taken.

- Risk Benefit Assessment

  Per the CDTL, "(t)he review of this NDA is based primarily on chemistry, manufacturing and controls data. However, there are deficiencies related to (1) Chemistry, manufacturing and controls and (2) unresolved safety issue. In addition, an overall acceptable recommendation is pending from the office of Compliance. Therefore, this application cannot be recommended for approval until all the above deficiencies are satisfactorily addressed, and an overall acceptable

recommendation is received from the Office of Compliance." It is noted that since the CDTL review was signed, an acceptable recommendation by EES has been submitted.

In addition, the clinical review states "(t)he magnitude and clinical significance of potential alcohol-related toxicities, and the difference between this docetaxel product and the referenced or other marketed docetaxel drug products, remains uncertain without additional clinical information." The Clinical Reviewer recommends that this 505(b)(2) resubmission receive a Complete Response based on the unresolved safety concern. This review is co-signed by the clinical Team Leader Virginia Maher MD.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  NA

- Recommendation for other Postmarketing Requirements and Commitments

  NA

Amna Ibrahim MD
Deputy Division Director
DOP1

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/s/

AMNA IBRAHIM
02/14/2013

Division Director Summary Review

Date	February 29, 2012
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
NDA #	202-356
Applicant Name	Pfizer Labs
Date of Submission	April 29, 2011
PDUFA Goal Date	February 29, 2012
Proprietary Name / Established (USAN) Name	Docetaxel Injection Concentrate/ docetaxel injection
Dosage Forms / Strength	solution for intravenous injection/ vials containing docetaxel 10 mg/mL with total of 20 mg, 80 mg/ 130 mg, or 200 mg docetaxel
Proposed Indication(s)	1. For the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy 2. For the adjuvant treatment of patients with operable node-positive breast cancer 3. As a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy 4. In combination with prednisone for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer 5. In combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease 6. In combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the dead and neck (SCCHN)
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	William Pierce
Pharmacology Toxicology Review	Haw-Jyh Chiu
ONDQA Review	Josephine Jee
Product Quality Microbiology Review	Steven Fong & John Metcalfe
Bioparmaceutics Review	Elsbeth Chikhale
Clinical Pharmacology Review	Lillian Zhang
CDTL Review	Sarah Pope
OPDP Review	Carole Broadnax
OSE/DMEPA	James Schlick
DMPP/OMPI	Barbara Fuller

OND=Office of New Drugs
ONDQA=Office of New Drug Quality
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OMPI=Office of Medical Policy Initiatives
DMPP+Division of Medical Policy Programs

Division Directory Summary Review

1. Introduction

Pfizer Labs submitted this new drug application for docetaxel injection for intravenous infusion for approval as an NDA under the provisions of 505(b)(2). This application relies upon FDA's previous findings of safety and efficacy for the listed drug, Taxotere 40 mg/mL (sanofi-aventis U.S. LLC), approved under NDA 20-449 on May 14, 1996. Differences between this drug and the listed drug, Taxotere, will be described in the background section of this review.

The biochemical comparison of the API between Pfizer's Docetaxel Injection (10 mg/mL) and Taxotere 40 mg/mL (sanofi-aventis) resulted in a determination that the requirement for bioequivalence studies could be waived allowing FDA reviewers to rely on the previous findings of safety and efficacy for Taxotere for non-clinical toxicology, clinical pharmacology, and clinical safety and efficacy findings. However, the quality reviewers identified numerous deficiencies in characterization of the drug product. These findings resulted in a recommendation that the NDA not be approved pending satisfactory resolution of the deficiencies, which included:

- Insufficient information to support the safety of the acceptance limits for impurities.
- Insufficient information to establish the safety of leachables in the proposed container/closure system.
- Insufficient information to establish the compatibility of the drug product, prepared in accordance with proposed product labeling, with syringes and intravenous tubing.
- Insufficient information to establish and support the proposed expiry dating period.

In addition, there are two unexpired patents for the listed drug, which would also preclude approval at this time.

2. Background

A Pre-NDA meeting was held November 1, 2010. Pfizer Labs stated their intent to file their proposed NDA as a 505(b)(2) application. In the premeeting package, Pfizer described their plans to submit a 505(b)(2) application for anhydrous docetaxel relying on Reference is made to Taxotere®, 40/mL, the listed drug manufactured by sanofi-aventis; this product was approved under NDA 20-449 on May 14, 1996. Pfizer's application will rely on FDA's findings of safety and effectiveness for Taxotere®.

In the meeting package, Pfizer outlined their proposal for a ready-to-use 10 mg/mL solution in a (b) (4) medical grade polypropylene vial, containing docetaxel injection (10 mg/mL) supplied in four presentations of 20 mg/2 mL, 80 mg/8 mL,

130 mg/13 mL, and 200 mg/20 mL. The active pharmaceutical ingredient (API) for Pfizer's product is docetaxel (anhydrous). Pfizer's drug product is a clear, colorless to brown-yellow solution packaged in 2 mL, (b) (4) polypropylene vials closed with (b) (4) rubber stoppers and oversealed with (b) (4) crimps and (b) (4) flip-off tops.

Pfizer stated that their docetaxel injection 10 mg/mL is a reformulation of the reference product Taxotere®. Pfizer further noted that preparation of the Taxotere formulation referenced in this application is intravenous administration is a 2-step process. Specifically, the original formulation of Taxotere® was supplied as a 2-component presentation consisting of one vial containing docetaxel injection and a second vial containing the diluent. In the first step, these components were admixed and in the second step, the solution containing 10 mg/mL of docetaxel was further diluted for intravenous administration. In contrast, Pfizer's Docetaxel Injection (containing 10 mg/mL of docetaxel) is a 1-vial formulation that does not require the pre-mix step and is ready for immediate dilution for intravenous administration and administration. As compared to the 4 strengths for the proposed Pfizer product (20 mg, 80 mg, 130 mg, and 200 mg), the 2-vial presentation of Taxotere is supplied in two strengths (20 mg and 80 mg).

Pfizer maintained that, as compared to Taxotere, the Pfizer drug product formulation has an identical level of docetaxel, a nearly identical level of polysorbate 80, an increased level of ethanol; the differences include the inclusion of (b) (4), citric acid and EDTA in the Pfizer formulation. In addition, the API for the Pfizer product is docetaxel (anhydrous) while the API for the listed product is docetaxel (trihydrate). Pfizer stated that once admixed with the diluent, the admixture formulation shows similar levels for each ingredient to the product formulation. Other differences from the listed drug include formulation as a ready-to-use solution for injection without prior dilution prior to intravenous infusion and the product container (plastic rather than glass vial).

As stated in the meeting package, Pfizer concluded that the proposed impurity acceptance criteria for their drug product, while higher than that observed in Taxotere®, should not impose additional safety concerns beyond those observed with the listed drug.

Key agreements and issues regarding the planned submission included the following:

- A decision as to whether to grant a biowaiver would be made by FDA following evaluation of the data contained in the NDA.
- The pre-meeting package contained insufficient information to determine if impurity levels in the proposed product were adequately justified. Pfizer will provide side-by-side comparisons of the impurity profiles for their Docetaxel Injection and the listed drug, Taxotere.
- Additional non-clinical studies would be required to justify impurity levels if the side-by-side comparison (bullet above) indicated significant differences in the impurity profiles.
- The application would provide comparability data for the two API manufacturers, (b) (4) and (b) (4)
- FDA noted that due to the differences in container (glass vial for the listed drug and plastic for the Docetaxel Injection), in order to support the proposed expiry date, Pfizer will need

to provide at least 12 months of real-time stability data, and the NDA should be amended to include 18-months of real-time stability data.

Application history

- Submitted April 29, 2011
- Acknowledgement letter issues May 16, 2011
- Filing letter issues July 6, 2011, informing applicant of the review designation (standard) and PDUFA goals for communication of major deficiencies and labeling comments
- August 5, 2011 information request letter issued requesting information needed to assess Pfizer's request for categorical exclusion. The letter identified the content and format of information to be provided on the plant-derived API.
- October 7, 2011 information request letter identifying major deficiencies with the application, including the inadequacy of one of the supporting Drug Master Files (DMF) to support the NDA and need for information on batch analyses, leachables and extractables, and in-use compatibility testing for the drug product as prepared for infusion.
- November 18, 2011 letter issued advising Pfizer that three additional DMFs cited in the NDA were inadequate to support the application.
- November 29, 2011 electronic mail request for a signed certification of notification of the patent holder(s) of the NDA filing.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer that the application cannot be approved until the deficiencies identified have been resolved. These deficiencies include:

- Insufficient information to support the safety of the acceptance limits for impurities.
- Insufficient information to establish the safety of leachables in the proposed container/closure system through the proposed expiry dating period.
- Insufficient information to establish the compatibility of the drug product, prepared in accordance with proposed product labeling, with syringes and intravenous tubing.
- Insufficient information to establish and support the proposed expiry dating period.

The proposed drug product is formulated with polysorbate 80 as a (b) (4), propylene glycol and ethanol as (b) (4), disodium edentate as (b) (4), and citric acid as pH adjustment. The proposed formulation contains higher levels of ethanol (40% v/v, compared with (b) (4)% v/v present in Taxotere), as well as polysorbate- 80 ((b) (4)% in Taxotere compared to (b) (4)% in the proposed formulation). In addition, the proposed formulation contains propylene glycol, disodium edentate, and anhydrous citric acid, which are not present in the listed drug.

There were no deficiencies in product quality microbiology identified during the review. With regard to manufacturing facilities, the Office of Compliance issued an "acceptable" recommendation. The ONDQA biopharmaceutics reviewer assessed data in the application in support of Pfizer's request for waiver of *in vivo* bioequivalence studies and granted this request.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical toxicology reviewer that the application cannot be approved at this time based on inadequate data to assess the safety of the proposed impurity specifications for the Docetaxel Injection drug product or of leachables present in the drug product for the proposed expiry dating period. The deficiencies precluding approval identified by the nonclinical toxicology reviewer will be conveyed to Pfizer Labs in the Complete Response letter.

FDA relied on the previous findings of safety and effectiveness for the listed drug in support of this NDA. Pfizer did not conduct new GLP-compliant, toxicology studies with docetaxel in support of this NDA. Four non-GLP studies were conducted to (1) compare the pharmacokinetic of a single intravenous dose of Docetaxel Injection and Taxotere (cross-over design) in dogs, (2) compare *in vitro* protein binding and micelle release of Docetaxel Injection and Taxotere in human and canine plasma, (3) evaluate local tolerance in rabbits, and (4) compare *in vitro* compatibility of Docetaxel Injection and Taxotere, with assessment of hemolysis.

The non-clinical reviewer noted that the proposed acceptance criteria for all identified impurities in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2% and that the NDA contained inadequate scientific justification for the levels of impurities proposed. The non-clinical toxicology reviewer has recommended that any impurity specifications that exceed the qualification limit be lowered to either meet the current ICH Q3B(R2) Guidance or to not exceed the levels detected in Taxotere® or to provide data to justify the proposed limits. These data may be obtained from literature or from additional nonclinical studies.

In response to a request for data necessary to support the safety of leachables (compounds that may leach from elastomeric or plastic components of the container closure system), Pfizer identified the following leachables which may be present in the drug product: (b) (4) Pfizer elected to provide a literature-based assessment of the safety of the estimated total daily intake of these leachables rather than conduct nonclinical animal toxicology studies to qualify the safety of the leachable concentrations under the proposed expiry dating period.

These data were considered inadequate to support the safety of the leachables in the drug product by the quality reviewer because

- Raw data were not provided;
- A description of the complete analytical procedures or methodologies used to detect these leachables was not provided; and
- Information regarding how and when these leachables were measured, and the basis for their proposed TDI values was not provided.

These data were considered inadequate to support the safety of the leachables in the drug product by the non-clinical toxicology reviewer because

- The data above had not been provided and

- The data provided in the original submission and as amended, is inadequate to establish the risks of these leachables when administered intravenously to patients

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding pharmacology issues that preclude approval. The application contained no clinical data and relies on FDA's prior finding of safety and effectiveness for the listed drug, Taxotere (sanofi-aventis, NDA 20-449). Minor comments on the proposed product labeling provided by the clinical pharmacology reviewer will be conveyed upon receipt of the resubmission providing a complete response to the CMC deficiencies that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the quality microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The NDA contained no clinical data and relies on FDA's prior finding of safety and effectiveness for the listed drug, Taxotere (sanofi-aventis, NDA 20-449). I concur with the findings of the medical reviewer that there are no outstanding issues with regard to efficacy that preclude approval.

8. Safety

The application contained no clinical data and relies on FDA's prior finding of safety and effectiveness for the listed drug, Taxotere (sanofi-aventis, NDA 20-449). I concur with the findings of the medical reviewer that there are no outstanding issues with regard to safety that preclude approval.

As stated in the November 1, 2010 pre-meeting, differences in the formulation between Pfizer Labs' Docetaxel Injection and the listed drug, Taxotere, may increase the risks of certain adverse drug reactions. Therefore, Pfizer has proposed the additions of the following language in Warnings and Precautions subsection 5.8 and in Patient Information (Section 17) and added a new subsection 5.11.

5.8 Neurologic Reactions

(b) (4)

[redacted]

(b) (4)

New subsection 5.11
"Alcohol content

(b) (4)

Section 17
Patient Counseling Information

- "Explain to patients the possible effects of the alcohol content in Docetaxel, including possible effects on the central nervous system, (b) (4)

Patient Information
5. (b) (4)

9. Advisory Committee Meeting

An advisory committee was not required for this application as no issues were raised that required expert scientific advice.

10. Pediatrics

This application was not reviewed by the PeRC; on June 22, 2011, Dr. Greeley informed the Division that the requirements of PREA do not apply to this product since the PeRC had determined that docetaxel (anhydrous) and docetaxel (trihydrate) are not different active pharmaceutical ingredients.

11. Other Relevant Regulatory Issues

Unresolved relevant regulatory issues include two unexpired patents for the listed drug (Taxotere® 40 mg/mL, sanofi-aventis U.S. LLC) and two patents which Pfizer, Inc. claims are "invalid, unenforceable, or will not be infringed" by the manufacture of Docetaxel Injection. These patents are listed below:

- Pfizer Inc. certifies that Patent No. 5,714,512 will expire on January 3, 2013.
- Pfizer Inc. certifies that Patent No. 5,750,561 will expire on January 3, 2013.\
- Pfizer Inc. certifies that Patent No. 5,438,072 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Docetaxel Injection, Intravenous Infusion (IV) for which this application is submitted.
- Pfizer Inc. certifies that Patent No. 5,698,582 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Docetaxel Injection, Intravenous Infusion (IV) for which this application is submitted.

12. Labeling

- Proprietary name: Pfizer has proposed to market the product under the under the name "Docetaxel Injection Concentrate". Although no concerns regarding this name were raised by OND reviewers, both the OSE/DMEPA and ONDQA reviewers have stated that the term "Concentrate" should not be used in the proprietary name.

- Physician labeling: Based on the CMC issues precluding approval at this time, comments on physician labeling from the OND and OPDP reviewers were deferred pending resubmission. The proposal to include new information in Warnings and Precautions and in Patient Counseling and Labeling Information may require additional justification.

- Carton and immediate container labels: Comments on carton and container labeling provided by the OSE/DMEPA reviewer will be conveyed to Pfizer Labs in the Complete Review letter. Issues identified include

  With regard to carton and immediate container labels:
  - Revise the statement "Made in Australia" to "(b) (4) ."

- Modify colors of carton/container labeling to minimize the risk of medication errors, taking into consideration that colors should not overlap between the (1) one-vial vs. two-vial formulations and (2) between the concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag. Since the color proposed for Pfizer's 200 mg/20 mL strength is similar to the red color currently utilized for the one-vial Taxotere 80 mg/4 mL product by Sanofi Aventis, FDA requested that Pfizer choose a different color for strength differentiation that does not overlap with the currently marketed 80 mg/4 mL one-vial Taxotere by Sanofi Aventis.
- Remove "Concentrate" from the established name, which could lead to confusion with the currently approved, two vial concentrate preparations for docetaxel which have two dilution steps.
- Change the color of "Docetaxel Injection" to black to make the name more prominent.
- Revise the statement "(b) (4)" to "For Intravenous Infusion Only" and bold the words "Infusion Only".
- Remove "(b) (4)" because it competes with other important information and clutters the labels and labeling.
- Change the statement "single-use" to "single-use vial".
- Highlight the "(10 mg/mL)" statement by placing it in a red color block background with "(10 mg/mL)" in white lettering wherever it appears on the container or carton labeling to provide emphasis on the concentration.

With regard to container labels:

- Place the volume, in mL, immediately in front of the statement "single use vial."
- Relocate the statement "Caution: Cytotoxic Agent" to the side panel of the 80 mg/8 mL, 130 mg/13 mL, and 200 mg/20 mL labels.
- Ensure there is one character space between "10" and "mg/mL" in the strength presentation.
- To highlight the difference between docetaxel products, add the following statement: Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions." Additionally, bold and box the statement.
- Consider using a different orientation for the layout of the information on the principal display panel in order to accommodate the above recommended revisions to the container labels. In addition, because the container labels are small, consider removing remove the statements "(b) (4) statements by applying 21 CFR 201.10 (h)(2)(i) for minimum label requirements.

With regard to general comments for carton labeling:

- In red color block and in white lettering, add "xx mg/xx mL (10 mg/mL)" to the top of all panels of the carton labeling as a continuous banner to provide further emphasis on the concentration of the product. Do not include the "New Strength and Preparation" banner found on the Hospira and Sandoz products.

- As a continuous banner in red color block and in white lettering add the statement: "Ready to add to infusion solution. Check concentration prior to preparation. See package insert for complete instructions."

With regard to one-count carton labeling:

- Place the volume, in mL, immediately in front of the statement "single use vial"

With regard to five-count carton labeling:

- Remove "(b) (4)" and combine with the statement below.
- Change the statement "(b) (4)." to "5 x XX mL single use vials; discard unused portion." Place the corresponding total volume here the XX is located (i.e., "5 x 2 mL single use vials; discard unused portion" for the 20 mg/2 mL carton and so forth). This statement should be located below the NDC numbers.

- Patient labeling: Based on the CMC issues precluding approval at this time, comments on proposed patient labeling from the OND and OMPI/DMPP reviewers were deferred pending resubmission.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response. I concur with the recommendations of the ONDQA (quality) and non-clinical toxicology review staff that the application should not be approved based on inadequate information to support the safety of Docetaxel Injection 10 mg/mL.

- Risk Benefit Assessment
  Based on biochemical comparisons, FDA has determined that Pfizer may rely on FDA's prior findings of safety and efficacy for the active pharmaceutical ingredient with the listed drug (Taxotere® 40 mg/mL, sanofi-aventis U.S. LLC) in support of Pfizer's NDA for Docetaxel Injection 10 mg/mL. However, the application contains insufficient information to support the safety of impurity profile for Docetaxel Injection, where these differ from the listed drug. In addition, there is insufficient information to characterize drug product stability, to evaluate and establish the safety of leachables arising from contact between the drug product and the container/closure system, to evaluate and establish the safety of compatibility of the drug product with syringes and IV tubing under the proposed conditions of use, and inadequate data to support the proposed NDA in the cross-referenced Drug Master File. Specific deficiencies in the NDA to be conveyed to Pfizer Labs are:

  (1) Inadequate scientific justification for the proposed levels of impurities in the Docetaxel Injection drug product, which exceed the ICH Q3B(R2 qualification limit of 0.2% and the levels detected in Taxotere.

(2) Lack of validated analytical procedures to identify, monitor, and quantify leached components in the drug product. In addition, the application lacks robust data (from nonclinical studies or published literature) to qualify the safety of the leached compounds (specifically (b) (4) at the concentrations detected at the end of the proposed expiry dating period for the drug product.

(3) Insufficient data to demonstrate the compatibility of the drug product with the proposed syringe and infusion line (e.g., polyethylene-lined administration) under conditions described in the proposed package insert.

(4) The cross-referenced master file [DMF (b) (4) ((b) (4))] does not contain adequate information to support the NDA.

(5) Lack of validated tests/test methods and appropriately qualified acceptance criteria in the drug product specification for the following
- Extractable Volume
- Osmolality
- pH
- Content of Ethanol
- Content of EDTA

(6) Insufficient information regarding the supplier of polypropylene vials used in each of the batches submitted for batch analyses or stability study.

(7) Insufficient data to support drug product stability and expiry dating.

(8) Inadequate testing for alcohol content and pH in the drug product stability protocol.

(9) Provide drug product stability data for the drug product stored in upright and inverted positions. The vial position is not clear in the stability data provided in Section 3.2.P.8.3 of your NDA. The comparison between upright and inverted positions is important to determine whether contact of the drug product with the closure results in extraction of chemical substances from the closure components or if adsorption and absorption of product components into the container/closure occurs.

(10) Include the tests for content of alcohol and pH in your drug product stability testing.

(11) Identify the supplier of polypropylene vials used in each of the batches submitted for batch analyses and primary stability study.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  There is no REMS for the listed drug and, based on the available information in this NDA, a REMS would not be required in order to approve this drug.

- Recommendation for other Postmarketing Requirements and Commitments

  The review team has not identified the need for post-marketing requirements of commitments. This issue will be revisited at the time of the resubmission responding to the Complete Response letter.

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/s/

PATRICIA KEEGAN
02/29/2012