CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202356Orig1s000

CHEMISTRY REVIEW(S)

NDA 202356

Docetaxel Injection

10 mg/mL

Pfizer, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 202356 – Resubmission

2. REVIEW #4

3. REVIEW DATE: 17-JAN-2014

4. REVIEWERS: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	29-APR-2011
Amendment – Respond to FDA: Additional Site Info.	20-MAY-2011
Amendment – Respond to FDA: Environmental Analysis	09-SEP-2011
Amendment – Correction to 356h form for address	10-NOV-2011
Amendment - Response to IR Letter dated 07-OCT-2011	01-DEC-2011
Resubmission – Response to 29-FEB-2012 C/R Letter	14-AUG-2012
Response to CMC IR dated 16-NOV-2012	07-DEC-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission – Response to 14-FEB-2013 C/R Letter	12-SEP-2013
Response to Clinical Pharmacology IR	05-NOV-2013
Response to Labeling IR	10-JAN-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc.
Address:	235 East 42nd Street New York, New York 10017
Representative:	Tricia Racanelli, Pharm.D Director Worldwide Safety and Regulatory
Telephone:	212-733-2530

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials,

Chemistry Review Data Sheet

Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: **10 mg/mL** (four vial sizes: 20 mg/2 mL, 80 mg/ 8mL, 130 mg/13 mL, and 200 mg/ 20 mL)

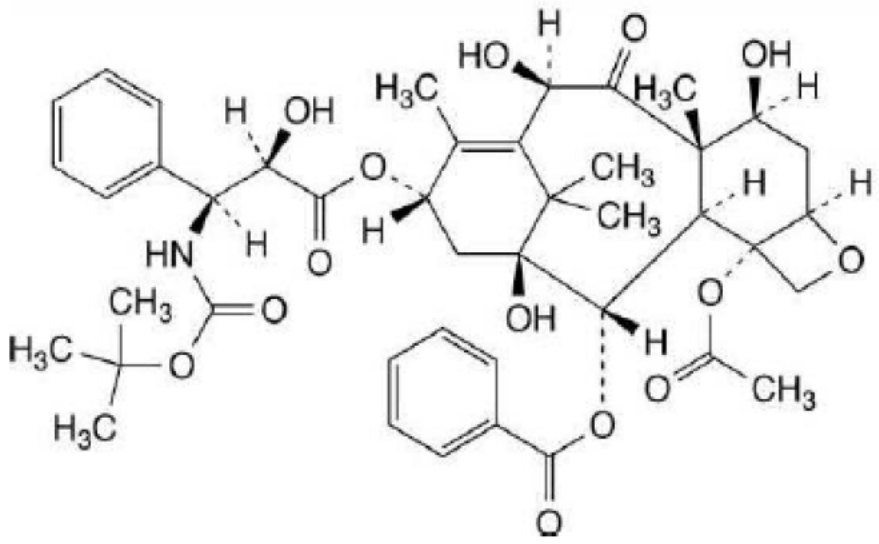
13. ROUTE OF ADMINISTRATION: Injection, Concentrate

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2(b)-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate



The empirical formula is: $C_{43}H_{53}NO_{14}$ The molecular weight: 807 (b) (4)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008 10-DEC-2009	By T. Ocheltree By D. Ghosh
	III			3	Adequate	10-JAN-2012	J. Jee
	III			1	Adequate	07-DEC-2012	J. Jee
	III			3	Adequate	20-JAN-2012	J. Jee
	III			3	Adequate	22-MAR-2009	R. Kasliwal
	V			1	Adequate	01-25-2012	S. Fong/J. Metcalfe

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
N/A			

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	17-AUG-2012	M. Stock	Acceptable on 13-DEC-2013
CLINICAL	Ethanol and Propylene Glycol	11-JAN-2013	W. Pierce	**Recommended C/R** based on the amount of ethanol and propylene glycol proposed in NDA 202356 formulation that may result in a difference in the safety profiles of the proposed Docetaxel Injection. Pending Recommendation as 17-JAN-2014.
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	14-JAN-2013	Haw-Jyh Chiu	See Pharm/Tox reviews dated 26-JAN-2012 and 14-FEB-2012, NDA 202356 in DARRTS. Resubmission – Recommends Approval
Biopharm	*In-vivo* Bioequivalence Waiver	19-NOV-2012	E. Chikhale	The in-vivo bioequivalence is granted and the recommendation is approval. See CMC BioPharm review dated 23-DEC-2011, and 19-NOV-2012 (Resubmission) NDA 202356 in DARRTS.
OSE/DMEPA	Labeling consult		J. Abdus-Samad	See DMEPA Review Resubmission - Pending
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Environmental Assessment	04-OCT-2011	Raanan Bloom	Acceptable. See Attachment 2 for Dr. R. Bloom response, email dated 04-OCT-2011.
Microbiology	(b) (4) manufacturing	25-JAN-2012	S. Fong/J. Metcalfe	Approval See Micro. Review dated 25-JAN-2012, NDA 202356 in DARRTS.

The Chemistry Review for NDA 202-356

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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)

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

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

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 or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. It should be noted that while the concentration of the reconstituted solution of the two-vial formulation of Taxotere® (the RLD) is 10 mg/mL (referenced in this NDA), the one-vial formulation of Taxotere® was approved on 02-Aug-2010 with a concentration of 20 mg/mL. The proposed undiluted Docetaxel Injection formulation contains docetaxel (anhydrous) as the active ingredient, docetaxel (trihydrate) is the active ingredient used in the innovator drug product, Taxotere®. In support of pharmaceutical equivalency between the two ingredients, Pfizer conducted and confirmed that both types of active ingredients are soluble in Pfizer's formulation up to three-fold the nominal concentration (i.e., 30 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 (b) (4), and citric acid as pH adjustment. Pfizer Docetacel Injection 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, Pfizer Docetaxel Injection contains propylene glycol, disodium edentate, and anhydrous citric acid that are not present in Taxotere Injection. 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) in contrast to the reference listed drug (RLD). The RLD is a 20 mg/mL. All four presentations are packaged in 2 mL, (b) (4), and 20 mL polypropylene vials closed with (b) (4) ((b) (4)) rubber stoppers and over sealed with (b) (4) crimps and (b) (4) flip-off seals. The vials are packaged in cartons with the prescribing information.

Note: The applicant proposed to use polypropylene vials manufactured from two different suppliers.

DMF [redacted] (b) (4) and DMF [redacted] (b) (4) are the suppliers of propylene vials. These DMFs were reviewed and found to be adequate (see p. 5 of this review).

The proposed drug product is manufactured by [redacted] (b) (4) The filled vials are tested for appearance, particulate matter, assay (HPLC), identification (HPLC and UV), chromatographic purity (HPLC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A 24-month expiry date is proposed based on 12 months of long term and 6 months of accelerated stability data.

Four specified impurities (same impurities identified in USP Monograph for Docetaxel Drug Substance) and one process impurity have been identified as carrying over from the drug substance into the drug product. The proposed maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B). Since, there is no official compendial monograph for docetaxel injection; the recommendation for acceptable levels in the impurities in docetaxel drug product would be based on the qualifications of each of the impurities or comparison of analytical results obtained from the proposed drug product with those obtained from the RLD. Pfizer's [redacted] (b) (4) analytical results are over two-fold higher than Pfizer results for [redacted] (b) (4) in Taxotere.

Note 1: The proposed drug product formulation is different from the RLD and the container is a polypropylene vial and in the RLD is a glass vial. Please refer to the Pharmacology/ Toxicology review dated 26-JAN-2012 for additional information regarding impurity qualification.
Pfizer provided on the 14-AUG-2012 Resubmission satisfactory impurities and leachables information to support the safety levels of these impurities. Please refer to the Pharmacology/ Toxicology review dated ***14-JAN-2013,*** which recommended approval.

Note 2: The proposed amount of ethanol and propylene glycol in the proposed Docetaxel Injection are higher than the RLD. W. Pierce, PharmD, Clinical Reviewer and V. Maher, MD, Clinical Team Leader stated: " The Applicant has created a new formulation of docetaxel that delivers a two- or three-fold increase in the amount of ethanol administered per dose compared to the ethanol that is delivered with each dose of the reference drug. The magnitude of this alcohol exposure exceeds the alcohol exposure of the previously approved docetaxel products currently marketed in the United States and maybe clinically relevant. When factoring in the potential additive effects and metabolic interactions between ethanol and propylene glycol, also unique to the Pfizer docetaxel formulation, additional intensification of alcohol-related toxicities is possible. The 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. 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". Please refer to the Clinical review dated 11-JAN-2013.

Pfizer provided on the 14-AUG-2012 Resubmission satisfactory compatibility information on validated analytical methods, analytical data obtained to support the safety levels of the identified leachables [redacted] (b) (4) in the proposed Docetaxel

Injection. The applicant provided supporting data to demonstrate the compatibility of the use of the syringe; however, there are no supporting data to demonstrate the acceptable use of the proposed infusion line under conditions described in the proposed package insert.
The proposed components and composition statement provided on 07-DEC-2012 list identically all four presentations which were bases on each mL. The proposed amounts of polysorbate-80, propylene glycol, and ethanol are reported as "approximately …"; these amounts should be exact in the proposed components and composition statement.
The drug product specification submitted on 07-DEC-2012 set the ethanol specification as (b)(4)% to (b)(4)%. The proposed amount of ethanol is approximated to be 40%. To represent a (b)(4)% to (b)(4)% should be (b)(4)% to (b)(4)%.

On 12-SEP-2013, the applicant provided acceptable components and composition statement for all four presentations, 20 mg/2 mL, 80 mg/ 8 mL, 130 mg/13 mL, and 200 mg/20 mL. Additionally, Pfizer provided acceptable acceptance criteria for ethanol content proposed at (b)(4)% w/v ((b)(4) – (b)(4)% w/v) and this test is included in the Post-Approval Stability Protocol and Stability Commitment. Lastly, the applicant provided acceptable compatibility and stability of Docetaxel dilution for infusion with the proposed polyethylene-lined administration sets under ambient room temperature and lighting conditions.

Drug Substance
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 (b)(4) impurity ((b)(4)) is formed by (b)(4). X-ray diffraction has identified (b)(4) morphic forms that are created when different solvents are used. It is reported that the desired morphic form (b)(4) is produced during manufacture via (b)(4).

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in (b)(4) ((b)(4)) bags, in (b)(4) bottle with (b)(4) (b)

The drug substance is sourced primarily from (b)(4) (DMF (b)(4)). Docetaxel drug substance sourced from (b)(4). (No DMF is referenced) was also used for the drug product development purposes only, and it was requested that Pfizer confirm the intent to use (or no longer use) (b)(4).

Note: On the 01-DEC-2011 Amendment, Pfizer has stated that they do not intend to use drug substance sourced from (b)(4).

There are no changes in Docetaxel Drug Substance since the submission dated 13-SEP-2013.

B. Description of How the Drug Product is Intended to be Used

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. The proposed indication is for locally

advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of prior to platinum-based chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, the treatment of advanced gastric cancer in combination with cisplatin and 5-fluorouracil, and the treatment of locally advanced, squamous cell head and neck cancer in combination with cisplatin and 5-fluorouracil.

C. Basis for Approvability or Not-Approval Recommendation

A detailed pharmaceutical development report and manufacturing process descriptions were provided in the NDA for the drug substance (DMF (b) (4)) and drug product. Adequate data have been provided to ensure the quality of the drug substance and drug product in the 12-SEP-2013 Submission.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling negotiations of the NDA. On 12-SEP-2013, Pfizer submitted acceptable labels and labeling. An overall acceptable recommendation from the Office of Compliance was issued dated 08-NOV-2013.

III. Administrative

This NDA was submitted in electronic as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS

C. CC Block

See DARRTS

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JOSEPHINE M JEE
01/24/2014

ALI H AL HAKIM
01/24/2014

CHEMISTRY REVIEWER MEMORANDUM

To:	NDA 202,356
From:	Josephine Jee, CMC Reviewer, ONDQA
Thru:	Nallaperumal Chidambaram, Ph.D., Acting Chief, Branch II
Date:	11-FEB-2013
Drug:	Docetaxel injection, 10 mg/mL
Route of administration:	Intravenously
Strength:	20 mg/2 mL, 80 mg/8 mL, 130 mg/13 mL, 200 mg/20 mL
Subject:	**Establishment Evaluation Recommendation**

Background

This review covers only the Establishment Evaluation for manufacturing facilities submitted by Pfizer, Inc dated 14-AUG-2012. For further information on NDA 202356, please refer to NDA 202356 CMC Review dated 11-DEC-2012, and 18-JAN-2013 (Update).

Note that though the Office of Compliance provided an overall acceptable recommendation for this application dated 08-FEB-2013, owing to a number of CMC deficiencies, a complete response action is recommended from the standpoint of chemistry, manufacturing, and controls (CMC).; see attached FDA CDER EES, Establishment Evaluation Request Summary Report.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202356/000	**Sponsor:**	PFIZER LABS
Org. Code:	150		235 EAST 42ND ST
Priority:	5		NEW YORK, NY 10017
Stamp Date:	29-APR-2011	**Brand Name:**	Docetaxel Injection Concentrate 10mg/mL
PDUFA Date:	14-FEB-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	16-DEC-2012	**Product Number; Dosage Form; Ingredient; Strengths**	

001; SOLUTION, INJECTION; DOCETAXEL; 20MG/2ML
002; SOLUTION, INJECTION; DOCETAXEL; 80MG/8ML
003; SOLUTION, INJECTION; DOCETAXEL; 130MG/13ML
004; SOLUTION, INJECTION; DOCETAXEL; 200MG/20ML

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	3017964023
	J. JEE	Review Chemist		3017961375
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	ACCEPTABLE	on 08-FEB-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 17-AUG-2012	by EES_PROD		
	ACCEPTABLE	on 11-JUL-2011	by M. STOCK	(HFD-320)	3017964753
	ACCEPTABLE	on 01-JUN-2011	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 25-MAY-2011	by EES_PROD		

Establishment:	**CFN:** 9612999	**FEI:** 3001415031	
	PFIZER PERTH PTY LTD. 15 BRODIE HALL DRIVE BENTLEY, PERTH, , AUSTRALIA		
DMF No:	16319	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-FEB-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4) (b) (4)		
DMF No:	(b) (4) (b) (4)	**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

JOSEPHINE M JEE
02/11/2013

NALLAPERUM CHIDAMBARAM
02/11/2013
I concur.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

lication:	NDA 202356/000	**Action Goal:**	
mp Date:	29-APR-2011	**District Goal:**	16-DEC-2012
jula	14-FEB-2013		
licant:	PFIZER LABS	**Brand Name:**	Docetaxel Injection Concentrate 10mg/mL
	235 EAST 42ND ST	**Estab. Name:**	
	NEW YORK, NY 10017	**Generic Name:**	
rity:	5	**Product Number; Dosage Form; Ingredient; Strengths**	
. Code:	150	001; SOLUTION, INJECTION; DOCETAXEL; 20MG/2ML 002; SOLUTION, INJECTION; DOCETAXEL; 80MG/8ML 003; SOLUTION, INJECTION; DOCETAXEL; 130MG/13ML 004; SOLUTION, INJECTION; DOCETAXEL; 200MG/20ML	

lication Comment: CLASS 2 RESUBMISSION DATED 8/14/12 (on 17-AUG-2012 by D. MESMER (HFD-800) 3017964023)

Contacts:				
	D. MESMER	Project Manager	(HFD-800)	3017964023
	J. JEE	Review Chemist		3017961375
	H. SARKER	Team Leader	(HFD-150)	3017961747

rall Recommendation:					
	PENDING	on 17-AUG-2012	by EES_PROD		
	ACCEPTABLE	on 11-JUL-2011	by M. STOCK	(HFD-320)	3017964753
	ACCEPTABLE	on 01-JUN-2011	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 25-MAY-2011	by EES_PROD		

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** 9612999 **FEI:** 3001415031

PFIZER PERTH PTY LTD.

15 BRODIE HALL DRIVE
BENTLEY, PERTH, , AUSTRALIA

F No: 16319 **AADA:**

ponsibilities: FINISHED DOSAGE MANUFACTURER

ablishment nment: DRUG SUBSTANCE AND DRUG PRODUCT RELEASE TESTING; DRUG PRODUCT MANUFACTURING, PACKAGING, LABELING, AND TESTING FACILITY (on 20-MAY-2011 by LAMBERTTU)

file: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
MITTED TO OC	25-MAY-2011				LAMBERTTU
MITTED TO DO	26-MAY-2011	10-Day Letter			TOULOUSEM
RECOMMENDATION	27-MAY-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
RECOMMENDATION	01-JUN-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
MITTED TO OC	17-AUG-2012				MESMERD
MITTED TO DO	20-AUG-2012	GMP Inspection			SAFAAIJAZIR
CL ` 2 RESUBMISSION DATED 8/14/12					
IGNED INSPECTION TO IB	02-SEP-2012	GMP Inspection			PHILPYE
PECTION SCHEDULED	16-OCT-2012		15-NOV-2012		IRIVERA
PECTION PERFORMED	13-DEC-2012		13-DEC-2012		Robert.Horan
See hard copy EIR.					

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

(b) (4)

(b) (4)

F No: (b) (4) **AADA:**

ponsibilities: DRUG SUBSTANCE MANUFACTURER

ablishment nment: DRUG SUBSTNACE MANUFACTURING AND TESTING FACILITY (on 20-MAY-2011 by LAMBERTTU)

file: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
MITTED TO OC	25-MAY-2011				LAMBERTTU
RECOMMENDATION	26-MAY-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
MITTED TO OC	17-AUG-2012				MESMERD
RECOMMENDATION	20-AUG-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

NDA 202356

Docetaxel Injection

10 mg/mL

Pfizer, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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Chemistry Review Data Sheet

1. NDA 202356 - Resubmission

2. REVIEW #3

3. REVIEW DATE: 11-DEC-2013/ 18-JAN-2013

4. REVIEWERS: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	29-APR-2011
Amendment – Respond to FDA: Additional Site Info.	20-MAY-2011
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6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission – Response to 29-FEB-2012 C/R Letter	14-AUG-2012
Response to CMC IR dated 16-NOV-2012	07-DEC-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc.
Address:	235 East 42nd Street New York, New York 10017
Representative:	Elina Srulevitch-Chin Executive Director, Portfolio Lead, Injectables Worldwide Regulatory Strategy
Telephone:	212-733-4471

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: **10 mg/mL** (four vial sizes: 20 mg/2 mL, 80 mg/ 8mL, 130 mg/13 mL, and 200 mg/ 20 mL)

13. ROUTE OF ADMINISTRATION: Injection, Concentrate

14. Rx/OTC DISPENSED: _X_Rx ___OTC

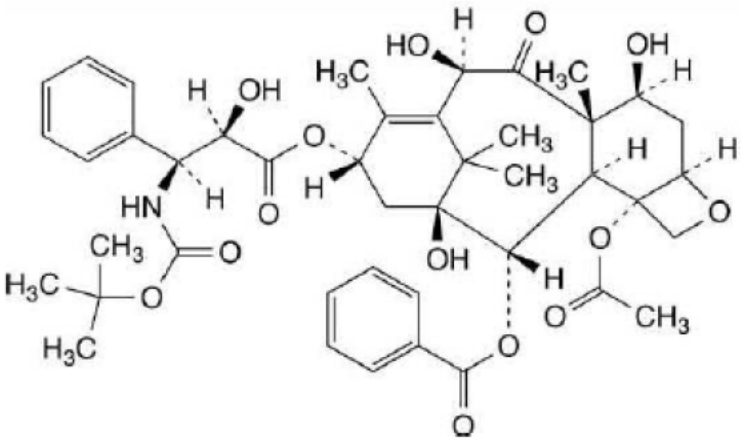
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(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



The empirical formula is: $C_{43}H_{53}NO_{14}$ The molecular weight: 807 (b)(4)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008 10-DEC-2009	By T. Ocheltree By D. Ghosh
	III			3	Adequate	10-JAN-2012	J.Jee
	III			1	Adequate	07-DEC-2012	J.Jee
	III			3	Adequate	20-JAN-2012	J.Jee
	III			3	Adequate	22-MAR-2009	R. Kasliwal
	V			1	Adequate	01-25-2012	S. Fong/J.Metclfe

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
N/A			

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	17-AUG-2012	M.Stock	Pending. Inspection scheduled for Pfizer Perth PTY Ltd, Perth, Australia
CLINICAL	Ethanol and Propylene Glycol	11-JAN-2013	W. Pierce	**Recommended C/R** based on the amount of ethanol and propylene glycol proposed in NDA 202356 formulation that may result in a difference in the safety profiles of the proposed Docetaxel Injection.
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	14-JAN-2013	Haw-Jyh Chiu	See Pharm/Tox reviews dated 26-JAN-2012 and 14-FEB-2012, NDA 202356 in DARRTS. Resubmission – Recommends Approval
Biopharm	*In-vivo* Bioequivalence Waiver	19-NOV-2012	E. Chikhale	The in-vivo bioequivalence is granted and the recommendation is approval. See CMC BioPharm review dated 23-DEC-2011, and 19-NOV-2012 (Resubmission) NDA 202356 in DARRTS.
OSE/DMEPA	Labeling consult	14-AUG-2012	J. Schlick	See DMEPA review dated 17-JAN-2012 under NDA 202356 in DARRTS. Resubmission - Pending
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Environmental Assessment	04-OCT-2011	Raanan Bloom	Acceptable. See Attachment 2 for Dr. R. Bloom response, email dated 04-OCT-2011.
Microbiology	(b) (4) manufacturing	25-JAN-2012	S. Fong/J. Metcalfe	Approval See Micro. Review dated 25-JAN-2012, NDA 202356 in DARRTS. Resubmission - Pending

The Chemistry Review for NDA 202-356

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is a Complete Response with respect to the chemistry, manufacturing, and controls (CMC). The overall recommendation from the Office of Compliance is listed in EES (attachment 1) as pending. The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in the review for DMF (b) (4). However, the concern of Type III DMF (b) (4) as an inactive DMF, has been resolved and DMF (b) (4) is currently acceptable; see DMF (b) (4) Review dated 07-DEC-2012. Approvability of this application will be based on the resolution of acceptable carton and container labels and package insert labeling; see review notes.

This review addresses to responses submitted by Pfizer on 14-AUG-2012 Resubmission and IR responses dated 07-DEC-2012.

Pfizer's responses submitted in the 14-AUG-2012 Resubmission and 07-DEC-2012 Amendment are included in this review. Pfizer satisfactorily responded to Comments Nos. 1, 3, 5, 8, and 9-13 (DMEPA Comments). Pfizer responded partially to Comments Nos. 2, 4, 6, 7 forwarded on Review # 2 dated 10-FEB-2012. New deficiencies have been identified; see below. See DMEPA comments on pp 33 to 34.

1. Revise the composition of Docetaxel Injection 10 mg/mL submitted on 07-DEC-2012 to reflect the exact amount of ethanol in %w/w or %w/v, this is an important excipient and cannot be approximated. In addition, provide true representative components and compositions (per vial not per mL) for each of the four proposed presentations. Similarly, propylene glycol and polysorbate-80 should list the exact amount required for the formulation per vial (e.g., 2 mL, 8 mL, 13 mL, and 20 mL vials).

2. Revise the acceptance criteria for ethanol content to be (b) (4)-(b) (4)% of the actual amount added in the components and composition statement (e.g., 40%v/v would be (b) (4)% - (b) (4)% v/v).

3. Include the test of alcohol content in the Post-Approval Stability Protocol and Stability Commitment and provide the stability data obtained for ethanol content.

4. Provide compatibility data for your drug product with the proposed infusion line(e.g., polyethylene-lined administration) under the conditions described in the proposed package.

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

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

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 or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. It should be noted that while the concentration of the reconstituted solution of the two-vial formulation of Taxotere® (the RLD) is 10 mg/mL (referenced in this NDA), the one-vial formulation of Taxotere® was approved on 02-Aug-2010 with a concentration of 20 mg/mL. The proposed undiluted docetaxel injection formulation contains docetaxel (anhydrous) as the active ingredient, docetaxel (trihydrate) is the active ingredient used in the innovator drug product, Taxotere®. In support of pharmaceutical equivalency between the two ingredients, Pfizer conducted and confirmed that both types of active ingredients are soluble in Pfizer's formulation up to three-fold the nominal concentration (i.e., 30 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 (b) (4), and citric acid as pH adjustment. Pfizer Docetacel Injection contains higher levels of ethanol (40% v/v, compared with (b) (4)% v/v present in Taxotere), and equivalent amount of polysorbate-80 ((b) (4)% in Taxotere compared to (b) (4)% in the proposed formulation). In addition, Pfizer Docetaxel Injection contains propylene glycol, disodium edentate, and anhydrous citric acid that are not present in Taxotere Injection. 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) in contrast to the reference listed drug (RLD). The RLD is a 20 mg/mL. All four presentations are packaged in 2 mL, (b) (4), and 20 mL polypropylene vials closed with (b) (4) rubber stoppers and oversealed with (b) (4) crimps and (b) (4) flip-off seals. The vials are packaged in cartons with the prescribing information.

Note: The applicant proposed to use polypropylene vials manufactured from two different suppliers. DMF (b) (4) is found to be adequate on 07-DEC-2012, and DMF (b) (4) is found to be adequate.

The proposed drug product is manufactured by (b) (4). The filled vials are tested for appearance, particulate matter, assay (HPLC), identification (HPLC and UV), chromatographic purity (HPLC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A 24 month expiry date is proposed based on 12 months of long term and 6 months accelerated stability data.

Four specified impurities (same impurities identified in USP Monograph for Docetaxel Drug Substance) and one process impurity have been identified as carrying over from the drug substance into the drug product. The proposed maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B). Since, there is no compendial monograph for docetaxel injection; the recommendation for acceptable levels in the impurities in docetaxel drug product would be based on the qualifications of each of the impurities or comparison of analytical results obtained from the proposed drug product with those obtained from the RLD. Pfizer's (b) (4) analytical results are over two-fold higher than Pfizer results for (b) (4) in Taxotere.

Note 1: The proposed drug product formulation is different from the RLD and the container is a polypropylene vial and in the RLD is a glass vial. Please refer to the Pharmacology/ Toxicology review dated 26-JAN-2012 for additional information regarding impurity qualification.

Pfizer provided on the 14-AUG-2012 Resubmission satisfactory impurities and leachables information to support the safety levels of these impurities. Please refer to the Pharmacology/ Toxicology review dated ***14-JAN-2013,*** which recommended approval.

Note 2: The proposed amount of ethanol and propylene glycol in the proposed Docetaxel Injection are higher than the RLD. W. Pierce, PharmD, Clinical Reviewer and V. Maher, MD, Clinical Team Leader stated: " The Applicant has created a new formulation of docetaxel that delivers a two- or three-fold increase in the amount of ethanol administered per dose compared to the ethanol that is delivered with each dose of the reference drug. The magnitude of this alcohol exposure exceeds the alcohol exposure of the previously approved docetaxel products currently marketed in the United States and maybe clinically relevant. When factoring in the potential additive effects and metabolic interactions between ethanol and propylene glycol, also unique to the Pfizer docetaxel formulation, additional intensification of alcohol-related toxicities is possible. The 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. 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". Please refer to the Clinical review dated 11-JAN-2013.

Pfizer provided on the 14-AUG-2012 Resubmission satisfactory compatibility information on validated analytical methods, analytical data obtained to support the safety levels of the identified leachables (b) (4) (b) (4) Injection. The applicant provided supporting data to demonstrate the compatibility of the use of the syringe; however, there are no supporting data to demonstrate the acceptable use of the proposed infusion line under conditions described in the proposed package insert.

The proposed components and composition statement provided on 07-DEC-2012 list identically all four presentations which were bases on each mL. The proposed amounts of polysorbate-80, propylene glycol, and ethanol are reported as "approximately …"; these amounts should be exact in the proposed components and composition statement.

The drug product specification submitted on 07-DEC-2012 set the ethanol specification as (b) (4)% to (b) (4)%. The proposed amount of ethanol is approximated to be 40%. To represent a (b) (4)% to (b) (4)% should be (b) (4)% to (b) (4)%.

Drug Substance

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. It is reported that the desired morphic form ([redacted] is produced during manufacture [redacted].

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in [redacted] bags, in [redacted] bottle with [redacted]

The drug substance is sourced primarily from [redacted] (DMF [redacted]). Docetaxel drug substance sourced from [redacted] (No DMF is referenced) was also used for the drug product development purposes only, and it was requested that Pfizer confirm the intent to use (or no longer use) [redacted] Drug Substance.

Note: On the 01-DEC-2011 Amendment, Pfizer has stated that they do not intend to use drug substance sourced from [redacted]

B. Description of How the Drug Product is Intended to be Used

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. The proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of prior to platinum-based chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, the treatment of advanced gastric cancer in combination with cisplatin and 5-fluorouracil, and the treatment of locally advanced, squamous cell head and neck cancer in combination with cisplatin and 5-fluorouracil.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of a C/R for NDA 202-356 is based on the need to provide satisfactory responses to the comments as outlined in I.A.

III. Administrative

This NDA was submitted in electronic as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS

C. CC Block

See DARRTS

23 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JOSEPHINE M JEE
01/30/2013

NALLAPERUM CHIDAMBARAM
01/30/2013
I concur.

CHEMISTRY REVIEW

NDA 202356

Docetaxel Injection

Pfizer, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

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Table of Contents

Chemistry Review Data Sheet

1. NDA 202356

2. REVIEW #2

3. REVIEW DATE: 10-FEB-2012

4. REVIEWERS: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (CMC)	29-APR-2011
Amendment – Respond to FDA: Additional Site Info.	20-MAY-2011
Amendment – Respond to FDA: Environmental Analysis	09-SEP-2011
Amendment – Correction to 356h form for address	10-NOV-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment - Response to IR Letter dated 07-OCT-2011	01-DEC-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc.
Address:	235 East 42nd Street New York, New York 10017
Representative:	Beatrice Curran Associate Director, Worldwide Regulatory Strategy
Telephone:	212-733-2061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: **10 mg/mL** (four vial sizes: 20 mg/2 mL, 80 mg/ 8mL, 130 mg/13 mL, and 200 mg/ 20 mL)

13. ROUTE OF ADMINISTRATION: Injection, Concentrate

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

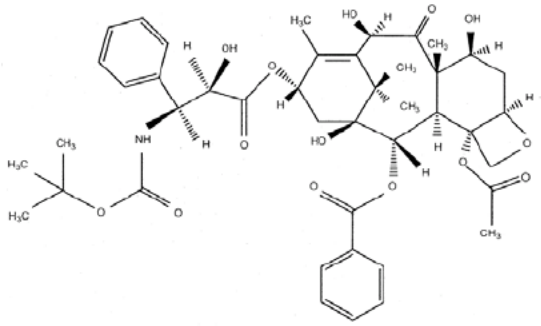
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(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



The empirical formula is: $C_{43}H_{53}NO_{14}$ The molecular weight: 807 (b)(4)

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008 10-DEC-2009	By T. Ocheltree By D. Ghosh
	III			3	Adequate	10-JAN-2012	J.Jee
	III			6	Not in Doc. RM	01-DEC-2011	See email dated 01-DEC-2011 between the Agency and the DMF Holder in DARRTS under DMF (b) (4)
	III			3	Adequate	20-JAN-2012	J.Jee
	III			3	Adequate	22-MAR-2009	R. Kasliwal
	V			1	Adequate	01-25-2012	S. Fong/J.Metclfe

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
N/A			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	23-OCT-2011	M.Stock	Acceptable. Overall re-evaluation on 01-MAR-2012 in EES.
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	26-JAN-2012	Haw-Jyh Chiu	See Pharm/Tox reviews dated 26-JAN-2012 and 14-FEB-2012, NDA 202356 in DARRTS.
Biopharm	*In-vivo* Bioequivalence Waiver	23-DEC-2011	E. Chikhale	The in-vivo bioequivalence is granted and the recommendation is approval. See CMC BioPharm review dated 23-DEC-2011, NDA 202356 in DARRTS.
OSE/DMEPA	Labeling consult	17-JAN-2012	J. Schlick	See DMEPA review dated 17-JAN-2012 under NDA 202356 in DARRTS.
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Environmental Assessment	04-OCT-2011	Raanan Bloom	Acceptable. See Attachment 2 for Dr. R. Bloom response, email dated 04-OCT-2011.
Microbiology	(b) (4) manufacturing	25-JAN-2012	S. Fong/J. Metcalfe	Approval See Micro. Review dated 25-JAN-2012, NDA 202356 in DARRTS.

The Chemistry Review for NDA 202-356

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is Complete Response with respect to the chemistry, manufacturing, and controls (CMC). The overall recommendation from the Office of Compliance is listed in EES (attachment 1) as acceptable. The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in the review for DMF (b) (4). However, the Type III DMF (b) (4) is an inactive DMF, which was communicated to the DMF Holder on 01-DEC-2011. Approvability is also based on the resolution of acceptable carton and container labels and package insert labeling; see comments below.

This review addresses to responses submitted by Pfizer on 01-DEC-2011. DMF (b) (4) Holder has not submitted any updates since the Agency communication dated 01-DEC-2011.

The applicant has not submitted compatibility studies performed for the compatibility of the drug product with the proposed syringe and infusion line under conditions described in the proposed package insert.

The issues of impurities in the drug product specification are outstanding; refer to Pharm/Tox review dated 26-JAN-2012.

The drug substance sourced from (b) (4) is withdrawn; therefore, deficiency # 1 cited in Review No. 1 is satisfactory.

The deficiencies #2-4 identified in Review No.1 remain outstanding as of the date of this review; see deficiencies 1-3 of this review. Deficiency No. 5 (harmonize drug product specification at product release and for use in stability studies) cited in Review No.1 was addressed partially by Pfizer. The outstanding issue is the acceptance criteria for the impurities; refer to Pharm/Tox review. Deficiencies #4-8 were not included in the 07-OCT-2011 IR letter, as they were not identified at that time. Due to irresolvable issues and the intended Complete Response action, deficiencies #4-8 were not subsequently conveyed to the Applicant.

Deficiencies #9-13 include recommendations from DMEPA's review dated 20-JAN-2012, relate to product labeling and were not conveyed during this review cycle.

The following deficiencies represent the outstanding issues for this NDA. Pfizer's responses submitted in the 01-DEC-2011 Amendment are included in this review.

1. It is noted that the Response to Query 2 submitted in 01-DEC-2011 Amendment did

not provide any validated analytical procedures to identify, monitor, and quantify leached components in the drug product. Appropriate acceptance criteria for the levels of leached compounds should be proposed. Provide analytical results from batch analyses and drug product stability data to support acceptable levels of [redacted] (b) (4) as identified leachables in the proposed drug product. Propose and submit acceptance criteria for the identified leachables based on the provided batch analyses and stability data.

2. Provide compatibility data that adequately supports the compatibility of the drug product with the proposed syringe and infusion line under the conditions described in the proposed package insert.

3. DMF [redacted] (b) (4) ([redacted] (b) (4)) is inadequate to support this NDA.

4. Include and propose the following tests, methods, and acceptance criteria in the drug product specification:
   a. Extractable Volume
   b. Osmolality
   c. pH
   d. Content of Ethanol
   e. Content of EDTA

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

6. Provide drug product stability data for the drug product stored in an 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.

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

8. Revise the statement "Made in Australia" to "Manufacture by Pfizer (Perth) Pty Ltd, Bentley WA, Australia".

9. General Comments for the Container Labels and Carton Labeling
   i. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors

due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:

- One-vial vs. two-vial formulations
- Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

The color you propose for your 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. Therefore, not only could the concentrations get confused but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a color for strength differentiation that does not overlap with the currently marketed 80 mg/4 mL one-vial Taxotere by Sanofi Aventis.

ii. Remove "Concentrate" from the established name. This could lead to confusion with the two vial concentrate preparations which have two dilution steps. Additionally, change the color of "Docetaxel Injection" to black to make the name more prominent.

iii. Revise the statement "(b) (4)" to "For Intravenous Infusion Only" and bold the words "Infusion Only". For example: "For Intravenous **Infusion Only**".

iv. Remove "(b) (4)" because it competes with other important information and clutters the labels and labeling.

v. Change the statement "single-use" to "single-use vial".

vi. 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 of the product.

10. Container Labels

i. Place the volume, in mL, immediately in front of the statement "single use vial" (see A.6 above). For example: "2 mL single use vial" on the 20 mg/2 mL product and so forth.

ii. 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.

iii. Ensure there is one character space between "10" and "mg/mL" in the strength presentation.

iv. 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.

v. 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. The Sandoz and Hospira marketed docetaxel container labels are a good resource on guidance for making changes to the Pfizer product to ensure patient safety. In addition, since the container labels are small like Hospira and Sandoz labels, the applicant may wish to remove the statements "Store between…", "Protect from light,…" and "Dosage and Use:…" statements by applying 21 CFR 201.10 (h)(2)(i) for minimum label requirements.

11. General Comments for Carton Labeling

i. 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. The Sandoz and Hospira marketed docetaxel products are a good resource on guidance for this change. Do not include the "New Strength and Preparation" banner found on the Hospira and Sandoz products.

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

12. Comments for One-Count Carton Labeling
See Comment B1 above.

13. General Comments for Five Count Carton Labeling

i. Remove "(b) (4)" and combine with the statement below.

ii. Change the statement "(b) (4)" to "5 x XX mL single use vials; discard unused portion." Place the corresponding total volume where 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.

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

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

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 or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. It should be noted that while the concentration of the reconstituted solution of the two-vial formulation of Taxotere® (the RLD) is 10 mg/mL (referenced in this NDA), the one-vial formulation of Taxotere® was approved on 02-Aug-2010 with a concentration of 20 mg/mL. The proposed undiluted docetaxel injection formulation contains docetaxel (anhydrous) as the active ingredient, docetaxel (trihydrate) is the active ingredient used in the innovator drug product, Taxotere®. In support of pharmaceutical equivalency between the two ingredients, Pfizer conducted and confirmed that both types of active ingredients are soluble in Pfizer's formulation up to three-fold the nominal concentration (i.e., 30 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 (b) (4), and citric acid as pH adjustment. Pfizer Docetacel Injection 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, Pfizer Docetaxel Injection contains propylene glycol, disodium edentate, and anhydrous citric acid that are not present in Taxotere Injection. 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) in contrast to the reference listed drug (RLD). The RLD is a 20 mg/mL. All four presentations are packaged in 2 mL, (b) (4) and 20 mL polypropylene vials closed with (b) (4) rubber stoppers and oversealed with (b) (4) crimps and (b) (4) flip-off seals. The vials are packaged in cartons with the prescribing information.

Note: The applicant proposed to use polypropylene vials manufactured from two different suppliers. DMF (b) (4), (b) (4), is an inactive DMF and DMF (b) (4) is found to be adequate. (b) (4) was notified of the status of DMF (b) (4) on 01-DEC-2011. As of 10-FEB-2012, the supplier has not submitted adequate CMC information, and the DMF remains inadequate to support this NDA.

The proposed drug product is manufactured by (b) (4) The filled vials are tested for appearance, particulate matter, assay (HPLC), identification (HPLC and UV), chromatographic purity (HPLC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A 24 month expiry date is proposed based on 12 months of long term and 6 months accelerated stability data.

Four specified impurities (same impurities identified in USP Monograph for Docetaxel Drug Substance) and one process impurity have been identified as carrying over from the drug substance

into the drug product. The proposed maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B). Since, there is no compendial monograph for docetaxel injection; the recommendation for acceptable levels in the impurities in docetaxel drug product would be based on the qualifications of each of the impurities or comparison of analytical results obtained from the proposed drug product with those obtained from the RLD. Pfizer's [redacted] analytical results are over two-fold higher than Pfizer results for [redacted] in Taxotere. Note: the proposed drug product formulation is different from the RLD and the container is a polypropylene vial and in the RLD is a glass vial. Please refer to the Pharmacology/ Toxicology review dated 26-JAN-2012 for additional information regarding impurity qualification.

The compatibility information submitted by Pfizer on 01-DEC-2011 was not satisfactory due to the absence of validated analytical methods, the absence of analytical data obtained to support the safety levels of the identified leachables [redacted] in the proposed Docetaxel Injection. Similarly, there are no supporting data to demonstrate the acceptable use of the proposed syringe and infusion line under conditions described in the proposed package insert.

Drug Substance

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. It is reported that the desired morphic form ([redacted]) is produced during manufacture via [redacted].

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in [redacted] ([redacted]) bags, in [redacted] bottle with [redacted]

The drug substance is sourced primarily from [redacted] (DMF [redacted]). Docetaxel drug substance sourced from [redacted] (No DMF is referenced) was also used for the drug product development purposes only, and it was requested that Pfizer confirm the intent to use (or no longer use) [redacted] Drug Substance.

Note: On the 01-DEC-2011 Amendment, Pfizer has stated that they do not intend to use drug substance sourced from [redacted].

B. Description of How the Drug Product is Intended to be Used

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. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of prior to platinum-based chemotherapy, the treatment of metastatic, hormone-

refractory prostate cancer in combination with prednisone, the treatment of advanced gastric cancer in combination with cisplatin and 5-fluorouracil, and the treatment of locally advanced, squamous cell head and neck cancer in combination with cisplatin and 5-fluorouracil.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of C/R for NDA 202-356 is based on the need to provide:

1. Provide complete information for polypropylene vials manufactured by the Holder of DMF (b) (4) identified in the application. Alternatively, the DMF needs to be updated with sufficient information to ensure adequacy to support the NDA.

2. Validated analytical methods and analytical data to support the safety levels of identified leachables found in Docetaxel Injection, 10 mg/mL.

3. Compatibility study results of the drug product with the proposed syringe and infusion line under conditions described in the proposed package insert.

4. Include and propose the following tests, methods, and acceptance criteria in the drug product specification:
   a. Extractable Volume
   b. Osmolality
   c. pH
   d. Content of Ethanol
   e. Content of EDTA

5. Identify supplier of polypropylene vials used in each of the batches submitted for batch analyses and stability study.

6. Provide drug product stability data for the drug product stored in upright and inverted positions.

7. Include the tests for content of alcohol, content of EDTA, and pH in your drug product stability testing.

8. Container, carton and package insert labeling changes (not conveyed in this review cycle).

III. Administrative

This NDA was submitted in electronic as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS

C. CC Block

See DARRTS

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/s/

JOSEPHINE M JEE
02/22/2012

SARAH P MIKSINSKI
02/23/2012

CHEMISTRY REVIEW

NDA 202356

Docetaxel Injection

Pfizer, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

-

Table of Contents

Chemistry Review Data Sheet

1. NDA 202356

2. REVIEW #1

3. REVIEW DATE: 20-JAN-2012

4. REVIEWERS: Josephine Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (CMC)	29-APR-2011
Amendment – Respond to FDA: Additional Site Info.	20-MAY-2011
Amendment – Respond to FDA: Environmental Analysis	09-SEP-2011
Amendment – Correction to 356h form for address	10-NOV-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc.
Address:	235 East 42nd Street New York, New York 10017
Representative:	Beatrice Curran Associate Director, Worldwide Regulatory Strategy
Telephone:	212-733-2061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel injection
Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3,5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Taxotere® (docetaxel) Injection, 20 mg and 80 mg vials, Sanofi Aventis, NDA 20-449

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: **10 mg/mL** (four vial sizes: 20 mg/2 mL, 80 mg/ 8mL, 130 mg/13 mL, and 200 mg/ 20 mL)

13. ROUTE OF ADMINISTRATION: Injection, Concentrate

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

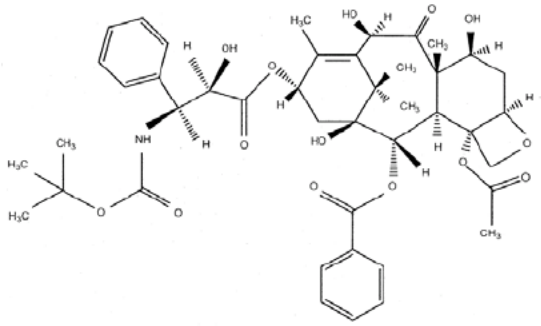
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(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



The empirical formula is: $C_{43}H_{53}NO_{14}$ The molecular weight: 807 (b)(4).

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II		(b) (4)	3	Adequate	08-JUL-2008 10-DEC-2009	By T. Ocheltree By D. Ghosh
	III			3	Adequate	10-JAN-2012	J.Jee
	III			6	Not in Doc. RM	Finalized - (b) (4)	DMF (b) (4) .msg
	III			3	Adequate	20-JAN-2012	J.Jee
	III			3	Adequate	22-MAR-2009	R. Kasliwal
	V			1	Adequate	01-25-2012	S. Fong/J.Metclfe

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
N/A			

18. CONSULTS/CMC-RELATED REVIEWS:

Chemistry Review Data Sheet

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	23-OCT-2011	M.Stock	Acceptable. Overall re-evaluation on 01-MAR-2012
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)		Haw-Jyh Chiu	Pending.
Biopharm	*In-vivo* Bioequivalence Waiver	23-DEC-2011	E. Chikhale	The in-vivo bioequivalence is granted and the recommendation is approval.
OSE/DMEPA	Labeling consult	17-JAN-2012	J. Schlick  Finalized - NDA 202356 Labeling R	See Comments
Methods Validation	N/A			Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Environmental Assessment	04-OCT-2011	Raanan Bloom  RE NDA 202356 response for EA.m	Acceptable
Microbiology	(b) (4) manufacturing		S. Fong/J. Metcalfe  RE DMF (b) (4) Deficiencies.msg	Approval

The Chemistry Review for NDA 202-356

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for the application is Complete Response with respect to the chemistry, manufacturing, and controls (CMC). The overall recommendation from the Office of Compliance is listed in EES (attachment 1) as acceptable. The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in the review for DMF (b) (4). However, the Type III DMF (b) (4) is an inactive DMF, which was communicated to the DMF Holder on 01-DEC-2011. Approvability is also based on the resolution of acceptable carton and container labels and package insert labeling; see comments below.

Amendment dated 01-DEC-2011 is not reviewed in this cycle due to absence of DMF (b) (4) information, and satisfactory compatibility data.

The following deficiencies #1-5 were identified in the review of the NDA submission, were communicated in an IR letter dated 07-OCT-2011, and remain outstanding as of the date of this CMC review. Deficiencies #6-9 were not included in the 07-OCT-2011 IR letter, as they were not identified at that time. Due to unresolvable issues and the intended Complete Response action, deficiencies #6-9 were not subsequently conveyed to the Applicant.

Deficiencies #10-12 include recommendations from DMEPA's review dated 20-JAN-2012, relate to product labeling and were not conveyed during this review cycle.

The Applicant's 01-DEC-2011 submission will be reviewed subsequently in this review cycle. Final deficiency language for the action letter will be proposed in CMC Review #2.

1. Batch analyses for Docetaxel Injection were submitted for product manufactured by Pfizer (Perth) Pty Ltd. using drug substance sourced from (b) (4). or (b) (4) (b) (4) Complete Chemistry, Manufacturing and Controls information for (b) (4) docetaxel drug substance was not provided in NDA 202356. Provide the complete CMC information or alternatively submit a statement to withdraw (b) (4) as a drug substance manufacturer.

2. Evaluate the drug product for compounds that may leach from elastomeric or plastic components of the container closure system. Establish appropriate validated analytical procedures to identify, monitor, and quantify leached components in the drug product, and propose acceptance criteria for the levels of leached compounds in the formulation. Additionally, provide the same information for the infusion solution in the syringe, plastic bag and infusion line recommended for the intravenous infusion of docetaxel

injection.

3. Provide in-use compatibility and stability data for the drug product as prepared for infusion.

4. DMF (b) (4) ((b) (4)) is currently inadequate to support your NDA. Inform your DMF holder and request that they contact Deborah Mesmer, Regulatory Project Manager for Quality, at the telephone number listed at the end of this letter.

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

6. Include and propose the following tests, methods, and acceptance criteria in the drug product specification:
   a. Extractable Volume
   b. Osmolality
   c. pH
   d. Content of Ethanol

7. Identify the supplier of polypropylene vials used in each of the batches submitted for batch analyses or stability study.

8. Provide drug product stability data for the drug product stored in an upright and inverted positions. It is not clear the position of 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 adsorption and absorption of product components into the container/closure.

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

10. Revise the statement "Made in Australia" to "Manufacture by Pfizer (Perth) Pty Ltd, Bentley WA, Australia".

11. General Comments for the Container Labels and Carton Labeling
    i. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between the following:
       • One-vial vs. two-vial formulations

- Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag

The color you propose for your 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. Therefore, not only could the concentrations get confused but the strengths could get confused as well. This could lead to wrong dose errors. Thus, we request you choose a color for strength differentiation that does not overlap with the currently marketed 80 mg/4 mL one-vial Taxotere by Sanofi Aventis.

ii. Remove "Concentrate" from the established name. This could lead to confusion with the two vial concentrate preparations which have two dilution steps. Additionally, change the color of "Docetaxel Injection" to black to make the name more prominent.

iii. Revise the statement "(b) (4)" to "For Intravenous Infusion Only" and bold the words "Infusion Only". For example: "For Intravenous **Infusion Only**".

iv. Remove "(b) (4)" because it competes with other important information and clutters the labels and labeling.

v. Change the statement "single-use" to "single-use vial".

vi. 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 of the product.

12. Container Labels

i. Place the volume, in mL, immediately in front of the statement "single use vial" (see A.6 above). For example: "2 mL single use vial" on the 20 mg/2 mL product and so forth.

ii. 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.

iii. Ensure there is one character space between "10" and "mg/mL" in the strength presentation.

iv. 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.

v. 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. The Sandoz and Hospira marketed docetaxel container labels are a good resource on guidance for making changes to the Pfizer product to ensure patient safety. In addition, since the container labels are small like Hospira and Sandoz labels, the applicant may wish to remove the statements "Store between…", "Protect from light,…" and "Dosage and Use:…" statements by applying 21 CFR 201.10 (h)(2)(i) for minimum label requirements.

13. General Comments for Carton Labeling

i. 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. The Sandoz and Hospira marketed docetaxel products are a good resource on guidance for this change. Do not include the "New Strength and Preparation" banner found on the Hospira and Sandoz products.

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

14. Comments for One-Count Carton Labeling
See Comment B1 above.

15. General Comments for Five Count Carton Labeling
i. Remove "(b) (4)" and combine with the statement below.

ii. Change the statement "(b) (4)." to "5 x XX mL single use vials; discard unused portion." Place the corresponding total volume where 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.

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

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Executive Summary Section

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 or dextrose) prior to patient administration. It was developed as a "ready-to-use" alternative to Taxotere® (docetaxel) Injection Concentrate (NDA 20-449), marketed by Sanofi Aventis. It should be noted that while the concentration of the reconstituted solution of the two-vial formulation of Taxotere® (the RLD) is 10 mg/mL (referenced in this NDA), the one-vial formulation of Taxotere® was approved on 02-Aug-2010 with a concentration of 20 mg/mL. The proposed undiluted docetaxel injection formulation contains docetaxel (anhydrous) as the active ingredient, docetaxel (trihydrate) is the active ingredient used in the innovator drug product, Taxotere®. In support of pharmaceutical equivalency between the two ingredients, Pfizer conducted and confirmed that both types of active ingredients are soluble in Pfizer's formulation up to three-fold the nominal concentration (i.e., 30 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 (b) (4), and citric acid as pH adjustment. Pfizer Docetacel Injection 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, Pfizer Docetaxel Injection contains propylene glycol, disodium edentate, and anhydrous citric acid that are not present in Taxotere Injection. 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) in contrast to the reference listed drug (RLD). The RLD is a 20 mg/mL. All four presentations are packaged in 2 mL, (b) (4), and 20 mL polypropylene vials closed with (b) (4) ((b) (4)) rubber stoppers and oversealed with (b) (4) crimps and plastic flip-off seals. The vials are packaged in cartons with the prescribing information.

Note: The applicant proposed to use polypropylene vials manufactured from two different suppliers. DMF (b) (4), (b) (4), is an inactive DMF and DMF (b) (4) (b) (4) is found to be adequate. (b) (4) was notified of the status of DMF (b) (4) on 01-DEC-2011. As of 20-JAN-2012, the supplier has not submitted adequate CMC information, and the DMF remains inadequate to support this NDA.

The proposed drug product is manufactured by (b) (4). The filled vials are tested for appearance, particulate matter, assay (HPLC), identification (HPLC and UV), chromatographic purity (HPLC), sterility (USP <71>), and bacterial endotoxins (USP <85>).

Docetaxel injection is stored at 20 to 25°C, protected from light. A 24 month expiry date is proposed based on 12 months of long term and 6 months accelerated stability data.

Four specified impurities (same impurities identified in USP Monograph for Docetaxel Drug Substance) and one process impurity have been identified as carrying over from the drug substance into the drug product. The proposed maximum acceptance levels for each of the specified impurities are greater than those recommended by ICH Q3(B). Since, there is no compendial monograph for docetaxel injection; the recommendation for acceptable levels in the impurities in docetaxel drug product would be based on the qualifications of each of the impurities or comparison of analytical results obtained from the proposed drug product with those obtained from the RLD. Pfizer's (b) (4) analytical results are over two-fold higher than Pfizer results for (b) (4) in

Taxotere. Note: the proposed drug product formulation is different from the RLD and the container is a polypropylene vial and in the RLD is a glass vial. Please refer to the Pharmacology/Toxicology review for additional information regarding impurity qualification.

Drug Substance

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 [(b) (4)] c impurity ([(b) (4)]) is formed by [(b) (4)]. X-ray diffraction has identified [(b) (4)] morphic forms that are created when different solvents are used. It is reported that the desired morphic form ([(b) (4)] is produced during manufacture [(b) (4)].

Due to its highly hygroscopic nature and the detrimental effect of water on the drug substance, it is double packed in [(b) (4)] ([(b) (4)]) bags, in [(b) (4)] bottle with [(b) (4)]

The drug substance is sourced primarily from [(b) (4)] (DMF [(b) (4)]). Docetaxel drug substance sourced from [(b) (4)] (No DMF is referenced) was also used for the drug product development purposes only, and it was requested that Pfizer confirm the intent to use (or no longer use) [(b) (4)].

B. Description of How the Drug Product is Intended to be Used

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. The and the proposed indication is for locally advanced or metastatic breast cancer, advanced or metastatic non-small cell lung cancer after failure of prior to platinum-based chemotherapy, the treatment of metastatic, hormone-refractory prostate cancer in combination with prednisone, the treatment of advanced gastric cancer in combination with cisplatin and 5-fluorouracil, and the treatment of locally advanced, squamous cell head and neck cancer in combination with cisplatin and 5-fluorouracil.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of C/R for NDA 202-356 is based on the need to provide:

1. Complete information for polypropylene vials manufactured by the Holder of DMF [(b) (4)] identified in the application. Alternatively, the DMF needs to be updated with sufficient information to ensure adequacy to support the NDA.

2. Compatibility data for Docetaxel Injection, 10 mg/mL with the polypropylene vials, stoppers.

3. Compatibility of the infusion solution in the syringe, plastic bag, and infusion line recommended for the intravenous infusion of docetaxel injection.

4. In-use compatibility and stability data for the drug product as prepared for infusion.

5. Complete CMC information or alternatively submit a statement to withdraw (b) (4) as a drug substance manufacturer.

6. Harmonize the proposed acceptance criteria to reflect a single specification for both release and shelf-life, and revise the proposed specification accordingly.

7. Include and propose the following tests, methods, and acceptance criteria in the drug product specification:
   a. Extractable Volume
   b. Osmolality
   c. pH
   d. Content of Ethanol

8. Container, carton and package insert labeling changes (not conveyed in this review cycle).

III. Administrative

This NDA was submitted in electronic (labeling section only) as a 505(b)(2) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS

C. CC Block

See DARRTS

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/s/

JOSEPHINE M JEE
01/25/2012

SARAH P MIKSINSKI
01/25/2012

NDA FILEABILITY CHECKLIST

NDA Number: 202356 **Applicant: Pfizer** **Stamp Date: 29-APR-2011**
Drug Name: Docetaxel Injection

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) _Yes_

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		6 – 9 M data are provided by the applicant. It is also based on the data provided by the DMF Holder. (b) (4) retest-period is requested
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Provided Stability data for DS (6-9M) and DP up to 12 M.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	*		* Included in the Process Validation.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Josephine Jee Date: June 2, 2011

Team Leader: L.Zhou/S.Pope Miksinski Date: June 2, 2011

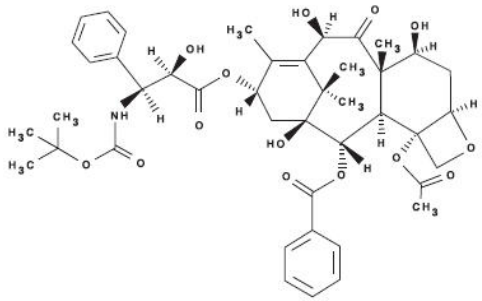
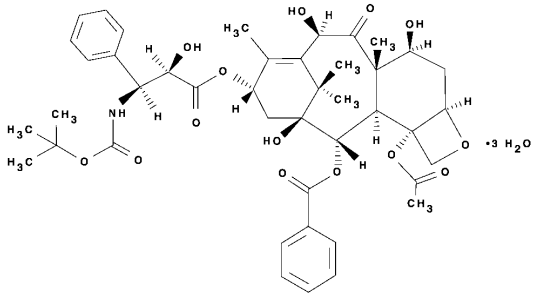
cc:
Original NDA 202356
DBOP/Division File
DBOP/S.Sickafuse
DBOP/P.Keegan
ONDQA/J.Jee
ONDQA/L.Zhou
ONDQA/S.Pope Miksinski
ONDQA/T. Lambert

NDA Number: 202356 **Applicant: Pfizer** **Drug Name: Docetaxel**

Have all DMF References been identified?

DMF Number	Holder	Description	LOA Included	Status
[redacted]	[redacted]	[redacted] (b) (4)	**Yes 17-SEP-2010**	**Pending Review**
			12-OCT-2010	**Pending Review**
			28-MAY-2010	**Pending Review**
			11-OCT-2010	**Pending Review**
			05-OCT-2010	**Pending Review**
			09-FEB-2011	**Pending Review**

NOTE:

Pfizer NDA proposes to use the anhydrous form	**TAXOTERE is a trihydrate form Sanofi-Aventis**
The chemical name for docetaxel (anhydrous) is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate M.W.: 807.9 White to almost white powder	The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate M.W.: 861.9 White to almost white powder
	

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/s/

JOSEPHINE M JEE
06/06/2011

LIANG ZHOU
06/07/2011

Initial Quality Assessment
Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

OND Division:	**Division of Biologic Oncology Products**
NDA:	20-2356 (e-submission)
Applicant:	Pfizer Labs C/O Pfizer Inc 50 Pequot Ave New London , CT 06320
Stamp Date:	29-April 2011
PDUFA Goal Date:	February 29, 2012 (Standard)
Established Name:	Docetaxel
Trade Name	Docetaxel
Dosage Form and Strength:	Injection; 10 mg/ mL
Route of Administration:	IV
Indication:	Breast Cancer; Non-Small Cell Lung Cancer; Prostate Cancer; Gastric Adenocarcinoma; Head and Neck Cancer
eCTD Reference for CMC:	NDA 20-2356 (Module 2 and 3)
Regulatory Filing	For 505 (b) (2)
Related IND/DMF	Pre-IND/Pre-NDA 109463
Assessed by	Liang Zhou, Ph.D.

	Yes	No
ONDQA Fileability:		x

See Recommendation in DS and DP sections.

Comments for 74-Day Letter:

Pending reviewer evaluation

Background Summary

Docetaxel is an antineoplastic agent belonging to the taxoid family. 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 binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown in vitro to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions. Docetaxel was found to be cytotoxic in vitro against various murine and human tumor cell lines and against freshly excised human tumor cells in clonogenic assays.

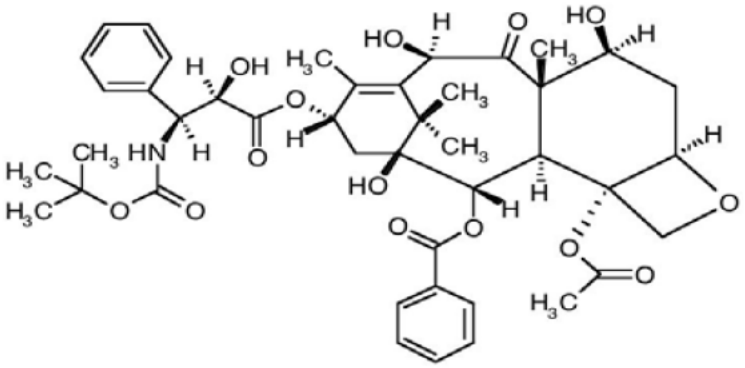
The RLD, Docetaxel (Taxotere®) injection by Sanofi Aventis was approved under NDA 20-449 (May 14, 1996), for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. It is noted that Taxotere® under NDA 20-449 is a solution formulation (40 mg base/mL), which is reconstituted with sterile WFI, USP.

Pfizer Docetaxel Injection (containing 10 mg/mL of docetaxel) is a single use vial formulation that does not require the pre-mix step and is ready for immediate dilution and administration. Pfizer Docetaxel Injection 10 mg/mL is filled in a single Cytosafe ® polypropylene vial. This 1-vial formulation will reduce the number of aseptic manipulations required to prepare the final infusion fluid, which may reduce the potential for contamination. The active pharmaceutical ingredient in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Taxotere. It also contains inactive ingredients commonly used in intravenous medications. The proposed indications for Pfizer Docetaxel Injection 10 mg/mL are identical to the indications used by Sanofi Aventis' Taxotere. Sanofi Aventis' Taxotere was marketed in a two-component system (the active ingredient is separated from the diluent), Pfizer's Docetaxel Injection 10mg/mL is a single-vial concentrate ready for dilution into an infusion solution.

IND 109463 pre-IND/pre-NDA meeting was held on November 11, 2010. The major CMC issues discussed are related to impurity profile of drug substance and drug product; stability data for a filling requirement and Bioequivalence waiver request. The CMC information of the NDA is submitted in CTDQ format.

Drug Substance (DS)

Docetaxel, a white to off-white powder, is freely soluble in polar organic solvents (ethanol, THF), and is insoluble in water. The structure of docetaxel is presented below (Figure 1). Docetaxel (b) (4) (b) (4) to yield the major (b) (4) impurity ((b) (4)). Docetaxel occurs in an anhydrous form, and polymorph screening studies resulted in additional identified morphic forms. The desired morphic form is produced during manufacture (b) (4). The active pharmaceutical ingredient (API) in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Sanofi Aventis Taxotere.



Molecular Structure in Figure 1

The drug substance, docetaxel (anhydrous), is sourced primarily from [(b) (4)] [(b) (4)]. Sections of the present regulatory filing for the drug substance which are specific to [(b) (4)] include the manufacturing process and process controls, impurity profiles, residual solvent profiles, batch analyses, container closure system, and stability profile. Further technical data for the drug substance, including the manufacturer's test methods, test method validation summaries, and updated stability data to support the (extended) retest periods are available from the manufacturer. The drug substance is also sourced from [(b) (4)], [(b) (4)]. Drug substance sourced from [(b) (4)] has been used for drug product development purposes only. Sections of the present regulatory filing for the drug substance which are specific to [(b) (4)] include the impurity profiles, residual solvent profiles, and batch analytical data, as assessed independently by Pfizer, using Pfizer's test methods.

All Chemistry, Manufacturing and Controls information for the drug substance has been cross referenced to DMF [(b) (4)]. An acceptable Letter of Authorization has been provided for this cross-reference. However, the principal starting materials for the manufacture of docetaxel (anhydrous) are [(b) (4)] (abbreviated as either [(b) (4)], or [(b) (4)]) and [(b) (4)] The manufacturing process information from the plant extraction should be provided to assure control of the impurity profile. Also, there may be additional manufacturing and control facilities due to the change in starting material. The applicant claims that further details of the starting material(s) are available from the manufacturer(s).

Stability information is provided in DMF [(b) (4)]. The applicant proposes [(b) (4)] re-test periods based on the available stability data generated at two different sites for storage at [(b) (4)]°C.

An EES request was submitted to the Office of Compliance for the proposed sites provided in this submission.

The proposed drug substance manufacturing sites are listed below:
Docetaxel bulk drug substance are manufactured and tested by:

(b) (4)

Release testing site:

Pfizer (Perth) Pty Limited
15 Brodie Hall Drive
Bentley WA 6102
Australia

Drug Substance Critical Issues

- The proposed starting materials are (b) (4), or (b) (4) and (b) (4). The manufacturing process information from the plant extraction should be provided to assure control of the impurity profile (e.g. manufacturing process information from the plant extraction including plant family and species, etc).
- Drug substance sourced from (b) (4) has been used for drug product development purposes only. all pertinent information bridged with the proposed (b) (4) DS need to be critically reviewed
- The active pharmaceutical ingredient in Docetaxel Injection Concentrate 10 mg/mL is docetaxel (anhydrous), instead of docetaxel (trihydrate) used in Sanofi Aventis Taxotere. The FDA drug classification (e.g. type 2 or/and 5) for this NDA needs to be carefully considered based on the regulation and draft Drug Classification Mapps. It seems that this DS can obtain 5 different crystal forms from different manufacturing process. It is not sure whether this anhydrous form is only resulted from a consistent manufacturing process control. If this is a new hydrate form of active pharmaceutical ingredient, I would recommend that the applicant needs to obtain an USAN name (also refer to the applicant's new CAS number for this anhydrous form) in order to accurately reflect DS characteristics on the Package Insert. Furthermore, as per USAN Guiding Principles, Appendix VII No. 12 as shown below:
  "A name for a substance generally should not indicate the state of hydration, morphology, or the mode of preparation. Reference to the water of hydration is retained in the chemical information as chemical name, formula and weight) but is excluded from the nonproprietary name. The degree of hydration becomes a part of the chemical entity identified by the USAN".
- Stability data for docetaxel and the applicant's drug substance stability program should be carefully assessed for adequacy, which is also relevant to its relation to drug product and final infusion solution stability.
- The applicant cross-references a Type II DMF (b) (4) for docetaxel manufacture and control. This DMF should be assessed for adequacy to support this NDA.
- Docetaxel is known to exhibit polymorphism. The applicant's ability to consistently produce a quality and specific morphic/anhydrous form of the drug substance should be confirmed during the review.

- EER information for drug substance needs to be re-examined for accuracy.
- OPS EA Consult (Environment Categorical Exclusion Claims) needs to be sent.

Drug Product (DP)

The proposed Docetaxel Injection Concentrate (Pfizer's product) is a clear colorless to brown-yellow solution. Docetaxel Injection Concentrate is sterile, non-pyrogenic, and is available in single-dose, Cytosafe® polypropylene vials containing 20 mg (2 mL), 80 mg (8 mL), 130 mg (13 mL) or 200 mg (20 mL) docetaxel (anhydrous). Each mL contains 10 mg docetaxel (anhydrous), 259 mg polysorbate 80, USP, 374 mg propylene glycol, USP, 0.01 mg edetate disodium, USP, (approximately) 3.5 mg anhydrous citric acid, USP, (b) (4) and 40% (v/v) dehydrated alcohol, USP.

Sanofi Aventis' product contains docetaxel as the active ingredient and (b) (4)% v/v ethanol and (b) (4)% v/v polysorbate 80 as inactive ingredient. The accompanying diluent consists (b) (4) sterile Water for Injection. The proposed Pfizer's Docetaxel Injection Concentrate contains high level of 40% v/v ethanol, (b) (4)% v/v propylene glycol, disodium edentate and anhydrous citric acid. The applicant claims that when the proposed Docetaxel Injection Concentrate diluted with Water for Injection, appears to be pharmaceutically equivalent to Sanofi Aventis' Taxotere® (docetaxel) Injection concentrate diluted with 13% ethanol in (b) (4) % v/v water based on osmolarity, blood compatibility, tolerance studies. Note that the blood compatibility and tolerance study need to be reviewed by non clinical review team and clinical review team, respectively. However, bioequivalence waiver request needs to be consulted to ONDQA Biopharm review team. ONDQA Biopharm team may need to work with the CMC review team as well other NDA discipline review teams for the bioequivalence waiver request. Note that as of today, FDA has not published or granted AP rating to Sanofi Aventis' Taxotere® in Orange Book. Therefore, the Agency's decision to grant bioequivalence waiver should be carefully considered. It should be noted that there are major formulation differences between approved Sanofi Aventis' Taxotere® formulation and the proposed Pfizer formulation such as unique physical characteristics of micelles, the solubility behaviors of active ingredient and EDTA (b) (4) used in the formulation.

The stability protocol is provided. The commercial presentations of Docetaxel Injection 10mg/mL are 20mg in 2mL, 80mg in 8mL, 130mg in 13mL and 200mg in 20mL, filled in medical-grade polypropylene vials, closed with a (b) (4) rubber stopper ((b) (4)) and sealed with an (b) (4) overseal with a (b) (4), flip-off top. The stability data generated to date support a 24 month shelf life for the drug product stored at/below 25°C, protected from light as follows:

Long term stability data from samples stored at 25°C /60% relative humidity (RH) and 30°C C/75%RH through 12 months have been generated. Accelerated stability data from samples stored at 40°C /75%RH through 6 months have also been generated. The photostability from one batch of the drug product is conducted. However, the adequacy of photostability studies needs to be reviewed.

The proposed expiry dating period is 24 months with storage at 25°C based on 12 months real time data.

The applicant states that all proposed manufacturing procedures are performed under cGMP.

The manufacture of Docetaxel Injection 10mg/mL will be carried out at the Pfizer facility in Perth, Australia. The responsibilities at this site are included for manufacturing, packaging, labeling and testing and release.

Pfizer (Perth) Pty Limited
15 Brodie Hall Drive
Bentley WA 6102
Australia

Drug Product Critical Issues

- This application requires a consult to the Office of Microbiology for the assessment of all aseptic and microbiological attributes, specifications, and manufacturing process details.
- Check EES of DP site for accuracy.
- OPS EA Consult is needed
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA (see Listed DMFs below Table)
- The labeling issues should be confirmed as part of the container/carton labeling review. The compatibility studies with the IV bags and diluent should be evaluated, and results should be captured in the Dose and Administration section. The description of DS needs to be evaluated if USAN name should be used in this section.
- Bioequivalence waiver request needs to be consulted to ONDQA Biopharm review team. ONDQA Biopharm review team also needs to work with the chemistry reviewer and BC as well other discipline review teams. This would require professional judgment and good discretion if Bioequivalence waiver is granted without reviewing PK/PD data in human.

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Comments and Recommendations

- The proposed starting material ((b) (4)) is unacceptable since (b) (4) is (b) (4). Thus, the information of manufacturing process for the (b) (4) , etc should be provided.

- The application is fileable. The proposed 24-months expiry dating periods for Docetaxel Injection Concentrate is supported by 12 months of long term stability data at recommended storage conditions.

- No other 74-Day Letter issues have been identified at this point. Facilities have been entered into EES for inspection. A single CMC reviewer has been assigned.

Liang Zhou, Ph.D. Chemistry, Manufacturing and Control Lead (CMC Lead)	June 1, 2011 Date
Sarah Pope Miksinski, Ph.D. Branch Chief	June 1, 2011, 2011 Date

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/s/

LIANG ZHOU
06/03/2011

SARAH P MIKSINSKI
06/03/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202356/000	**Action Goal:**	
Sta Date:	29-APR-2011	**District Goal:**	12-JAN-2014
Regulatory:	13-MAR-2014		
Applicant:	PFIZER LABS 235 EAST 42ND ST NEW YORK, NY 10017	**Brand Name:** **Estab. Name:** **Generic Name:**	DOCETAXEL INJECTION CONCENTRATE 10MG/ML DOCETAXEL INJECTION
Priority:	5	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	003; SOLUTION, INJECTION; DOCETAXEL; 130MG/13ML 002; SOLUTION, INJECTION; DOCETAXEL; 80MG/8ML 001; SOLUTION, INJECTION; DOCETAXEL; 20MG/2ML 004; SOLUTION, INJECTION; DOCETAXEL; 200MG/20ML	

Application Comment: CLASS 2 RESUBMISSION DATED 8/14/12 (on 17-AUG-2012 by D. MESMER (HFD-800) 3017964023)

FDA Contacts:				
	J. JEE	Prod Qual Reviewer		3017961375
	J. METCALFE	Micro Reviewer	(HFD-805)	3017961576
	T. AGOSTO	Product Quality PM		2404023777
	C. COTTRELL	Regulatory Project Mgr	(HFD-150)	3017964256
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	ACCEPTABLE	on 08-NOV-2013	by T. SHARP	()	3017963208
	PENDING	on 07-NOV-2013	by EES_PROD		
	ACCEPTABLE	on 08-FEB-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 17-AUG-2012	by EES_PROD		
	ACCEPTABLE	on 11-JUL-2011	by STOCKM		
	ACCEPTABLE	on 01-JUN-2011	by STOCKM		
	PENDING	on 25-MAY-2011	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9612999 **FEI:** 3001415031

PFIZER PERTH PTY LTD.

15 BRODIE HALL DRIVE
BENTLEY, PERTH, , AUSTRALIA

DMF No: 16319 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE AND DRUG PRODUCT RELEASE TESTING; DRUG PRODUCT MANUFACTURING, PACKAGING, LABELING, AND TESTING FACILITY (on 20-MAY-2011 by LAMBERTTU)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	25-MAY-2011				LAMBERTTU
SUBMITTED TO DO	26-MAY-2011	10-Day Letter			TOULOUSEM
DO RECOMMENDATION	27-MAY-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	01-JUN-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	17-AUG-2012				MESMERD
SUBMITTED TO DO CLASS 2 RESUBMISSION DATED 8/14/12	20-AUG-2012	GMP Inspection			SAFAAIJAZIR
AS ED INSPECTION TO IB	02-SEP-2012	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	16-OCT-2012		15-NOV-2012		IRIVERA
INSPECTION PERFORMED See hard copy EIR.	13-DEC-2012		13-DEC-2012		Robert.Horan
DO RECOMMENDATION	08-FEB-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	08-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR
SUBMITTED TO OC	07-NOV-2013				AGOSTOT
SUBMITTED TO DO PDUFA GOAL DATE: 13-MAR-2014 10-DAY - FDF	07-NOV-2013	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION INSPECTION CONDUCTED (b) (4) AND CLASSIFIED VAI. PAI FOR NDA 202356 AND (b) (4) (b) (4).	08-NOV-2013			ACCEPTABLE INSPECTION	TUNGL
OC RECOMMENDATION	08-NOV-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

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

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTNACE MANUFACTURING AND TESTING FACILITY (on 20-MAY-2011 by LAMBERTTU)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	25-MAY-2011				LAMBERTTU
OC RECOMMENDATION	26-MAY-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	17-AUG-2012				MESMERD
OC RECOMMENDATION	20-AUG-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR
SUBMITTED TO OC	07-NOV-2013				AGOSTOT
OC RECOMMENDATION	07-NOV-2013			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR