CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 201023/000	**Action Goal:**	
Stamp Date:	31-MAR-2010	**District Goal:**	24-MAY-2010
R itory:	30-SEP-2010		
Applicant:	SANOFI AVENTIS SPA	**Brand Name:**	CABAZITAXEL (XRP6258)
	55 CORORATE DR	**Estab. Name:**	
	BRIDGEWATER, NJ 08807	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; SOLUTION, CONCENTRATE; CABAZITAXEL; 60MG/1.5ML	

Application Comment: PRIORITY PROSTATE CANCER NDA WITH SHORTENED REVIEW CLOCK- 8 WEEK REVIEW CLOCK. REQUEST COMPLIANCE OVERALL RECOMMENDATION BY 5/24/10 (on 08-APR-2010 by D. MESMER (HFD-800) 301-796-4023)

FDA Contacts:				
	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	X. CHEN	Review Chemist		301-796-1337
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:	ACCEPTABLE	on 03-MAY-2010	by M. STOCK	(HFD-320)	301-796-4753

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Estab. Comment: (b) (4)

Profile: **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-APR-2010				MESMERD
OC RECOMMENDATION	21-APR-2010			ACCEPTABLE	STOCKM
				BASED ON FILE REVIEW	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610119 **FEI:** 3002808000

AVENTIS PHARMA LTD.

9 QUAL JULES GUESDE
VITRY-SUR-SEINE, , FRANCE

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

Responsibilities: DRUG SUBSTANCE LABELER

DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STERILITY TESTER

Estab. Comment: EMAIL FROM ELIZABETH PHILPY ON 4/7/10 INSTRUCTS THAT INFORMATION SUBMITTED FOR BOTH SANOFI-AVENTIS RECHERCHE & DÉVELOPPEMENT AT 13 QUAI JULES GUESDE AND SANOFI CHIMIE AT 9 QUAI JULES GUESDE SHOULD BE SUBMITTED UNDER THIS FEI NUMBER, 3002808000. SPONSOR INDICATES AT #13 QUAI JULES GUESDE: MANUFACTURING OF THE DRUG SUBSTANCE FROM (b) (4) AND (b) (4) AND MICROBIAL CONTAMINATION TESTING OF THE DRUG SUBSTANCE
AT 9 QUAI JULES GUESDE: TESTING AND RELEASE OF (b) (4)
TESTING AND RELEASE, PACKAGING AND LABELING OF THE DRUG SUBSTANCE.
CONTACT NAME FOR #13 IS :MARIE-PIERRE IMBERT
QUALITY ASSURANCE MANAGER
MARIE-PIERRE.IMBERT@SANOFI-AVENTIS.COM
TEL: 33.1.58.93.88.66
FAX: 33.1.58.93.30.61 (on 07-APR-2010 by D. MESMER (HFD-800) 301-796-4023)
PLEASE REFER TO FACTS ASSIGNMENT IDS 1157497 AND 1157501, WHICH WERE ISSUED FOR THIS PRODUCT PRIOR TO SUBMISSION DUE TO THE EXPEDITED STATUS OF THE APPLICATION. (on 09-APR-2010 by M. STOCK (HFD-320) 301-796-4753)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-APR-2010				MESMERD
SUBMITTED TO DO	09-APR-2010	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	16-APR-2010	Product Specific			JOHNSONE
DO RECOMMENDATION	03-MAY-2010			ACCEPTABLE	STOCKM
EXPEDITED COMPLIANCE REVIEW DONE BY DOUG CAMPBELL.				INSPECTION	
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610433 **FEI:** 1000541557

AVENTIS PHARMA LTD.

RAINHAM ROAD SOUTH
DAGENHAM, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: MANUFACTURING, TESTING AND RELEASE, PACKAGING AND LABELING OF THE DRUG PRODUCTS (CABAZITAXEL CONCENTRATE FOR SOLUTION FOR INFUSION AND SOLVENT FOR DILUTION) (on 07-APR-2010 by D. MESMER (HFD-800) 301-796-4023)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-APR-2010				MESMERD
SUBMITTED TO DO	08-APR-2010	10-Day Letter			STOCKM
DO RECOMMENDATION	16-APR-2010			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	18-APR-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610721 **FEI:** 1463

SANOFI AVENTIS PHARMA SA

63480
VERTOLAYE, , FRANCE

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

Responsibilities: INTERMEDIATE MANUFACTURER

Estab. Comment: MANUFACTURING OF (b) (4) FROM BEPIME (RPR106926)
TESTING AND RELEASE OF (b) (4) (on 07-APR-2010 by D. MESMER (HFD-800) 301-796-4023)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-APR-2010				MESMERD
OC RECOMMENDATION	09-APR-2010			ACCEPTABLE	STOCKM
				BASED ON FILE REVIEW	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

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

(b) (4)

Di. .to: **AADA:**

Responsibilities: INTERMEDIATE MANUFACTURER

Estab. Comment: MANUFACTURING (b) (4)
ADDRESS PROVIDED BY APPLICANT:
SERIPHARM SA (NOVASEP)
(b) (4)
(b) (4)

ESTABLISHMENT NUMBER PROVIDED BY APPLICANT (b) (4)

(on 08-APR-2010 by D. MESMER (HFD-800) 301-796-4023)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-APR-2010				MESMERD
OC RECOMMENDATION	21-APR-2010			ACCEPTABLE	STOCKM
				BASED ON FILE REVIEW	

ONDQA Division Director's Memo
NDA 201-023, JEVTANA (cabazitaxel) Injection
40 mg/mL supplied as 60 mg/1.5mL
Date: 04-JUN-2010

Introduction

JEVTANA (cabazitaxel) Injection is indicated for the treatment of metastatic prostate cancer that has progressed after docetaxel-based treatments. The drug product is supplied as a non-aqueous solution which is diluted with a co-packaged diluent at the time of administration. This pre-mix dilution is then added to normal saline for injection or D5W for intravenous infusion. **ONDQA recommends approval of this NDA.**

Administrative

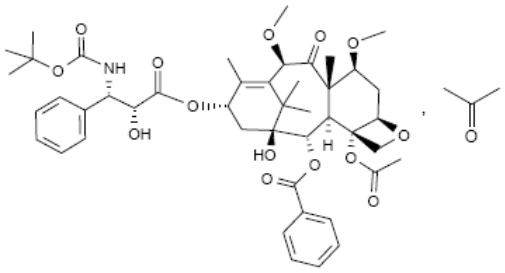
The original submission of this 505(b)(1) NDA was received 25-FEB-2010 from Sanofi-Aventis, Bridgewater, NJ. This priority review was also given a highly accelerated review status in light of the critical medical need cited by DDOP.

A total of seven CMC amendments were reviewed between 12-MAR-2010 and 28-MAY-2010. The NDA is supported by nine DMF's and by IND 56,999. Consults for PAI (EES acceptable -8-APR-2010), PharmTox, and EA are acceptable.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Drug Substance

The APi is cabazitaxel which contains a nearly stoiciometric molecule of acetone as the solvate in the solid (lyophilized) state. The name is:
benzenepropanoic acid, β -[[(1,1-dimethylethoxy)carbonyl]amino]-α -hydroxy-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12bdodecahydro-11-hydroxy-4,6-dimethoxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester,(α R, β S)-



Molecular formula: $C_{45}H_{57}NO_{14}$. C_3H_6O

Molecular weight: 894.01 (for the acetone solvate); 835.93 (for the non solvated form)

ACTION LETTER NOTE: The approved drug substance retest interval to be conveyed to the sponsor is (b) (4)

Drug Product.

The drug product is supplied as a non aqueous solution (60 mg cabazitaxel in 1.5mL polysorbate-80) and a co-packaged diluent (13% Ethanol in WFI).

The diluent vial contents are added to the drug containing vial (both are glass vials with rubber stoppers) and mixed gently (to avoid precipitation). This pre-mix solution is supersaturated by about 400% and is inherently physically unstable. It is labeled to be used immediately. The applicant has not adequately characterized the nucleation and kinetics of precipitation (which is known to occur). The in-use handling of the pre-mix has not been adequately supported by data.

ACTION LETTER NOTE: A post marketing requirement (PMR) is to be conveyed to the applicant to resolve this pre-mix issue within six months of approval

The pre-mix solution is added to the infusion vehicle (NS or D5W) which is also supersaturated, also by about 400%. This infusion solution has not adequately characterized regarding the nucleation and kinetics of cabazitaxel precipitation (which is known to occur). The in-use handling and storage of the infusion solution (24 hours refrigerated, 8 hours room temperature) has not been adequately supported by data.

ACTION LETTER NOTE: A post marketing requirement (PMR) is to be conveyed to the applicant to resolve this infusion solution issue within six months of approval

Given the important therapeutic nature of this drug product, and the fact that patients survive longer when given this drug; these drug product deficiencies may be managed post approval within six months as PMRs.

The drug product is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) Do not refrigerate.. An 18-month expiry period is recommended to be approved.

Rik Lostritto, Director, ONDQA Division I

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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

/s/

RICHARD T LOSTRITTO
06/08/2010

NDA 201-023

JEVTANA (cabazitaxel) Injection

Sanofi-aventis U.S. Inc.

Xiao-Hong Chen, Ph.D.

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

CMC Review of NDA 201-023

For the Division of Drug Oncology Products (HFD-150)

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-023

2. REVIEW #1

3. REVIEW DATE: 02-June-2010

4. REVIEWERS: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 56,999	21-MAY-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-FEB-2010
Amendment	12-MAR-2010
Amendment	17-MAR-2010
Amendment	16-APR-2010
Amendment	07-MAY-2010
Amendment	21-MAY-2010
Amendment	25-MAY-2010
Amendment	28-MAY-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Sanofi-Aventis U.S. Inc.
on behalf of sanofi-aventis U.S. LLC

Chemistry Review Data Sheet

Address:	55 Corporate Drive Bridgewater, NJ 08807
Representative:	Linda Gustavson, PhD, RAC
Telephone:	610-889-8246

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Cabazitaxel (USAN: application pending)
Code Name/# (ONDQA only): RPR116258A (RPR116258, acetone solvate), XRP6258
Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Metastatic prostate cancer that progressed on or after docetaxel-based treatment

11. DOSAGE FORM: Concentrate for solution for infusion

12. STRENGTH/POTENCY: 60 mg/1.5 mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_Rx ___OTC

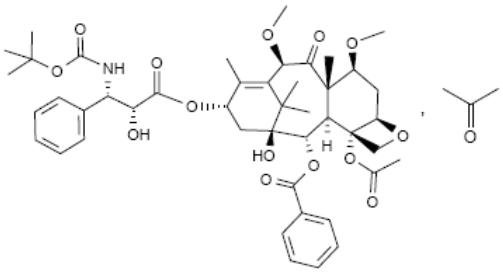
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

benzenepropanoic acid, β -[[(1,1-dimethylethoxy)carbonyl]amino]-α -hydroxy-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12bdodecahydro-11-hydroxy-4,6-dimethoxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester,(α R, β S)-



Molecular formula: $C_{45}H_{57}NO_{14} \cdot C_3H_6O$

Molecular weight: 894.01 (for the acetone solvate); 835.93 (for the solvent free)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	Sanofi Chimie	XRP6258 cabazitaxel acetone solvate	1	Adequate	06/02/2010	Reviewed by Brian Rogers
	II	Sanofi Chimie	(b) (4)	1	Adequate	06/02/2010	Reviewed by Brian Rogers
	II			3	Adequate	10/28/2008	Reviewed by by Chengyi Liang
	II			N/A	N/A	N/A	Withdrawn from the application.
	II			1	Adequate	06/02/2010	Reviewed by Brian Rogers
	III			4	N/A	Date of this review	See section 3.2.P.7
	III			4	N/A	Date of this review	See section 3.2.P.7
	III			4	N/A	Date of this review	See section 3.2.P.7
	III			1	Adequate	5/20/10	Reviewed by Sue-Ching Lin
				3	Adequate	4/12/07	Reviewed by Mark Sassaman
				3	Adequate	3/23/07	Reviewed by Mark Sassaman*

*There was a typographical error in the spelling of (b) (4). (b) (4) in the 3/23/07 review. It was incorrectly spelled as (b) (4)

[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

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	56,999	Sanofi	
NDA	20449	Sanofi	

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EES	Site inspections	8-APR-2010	Acceptable	OC recommendation received on 3-MAY-2010
Pharm/Tox	DS and DP Impurity	20-NOV-2009	Acceptable	Consult through email. Refer to Dr. Sachia Khasar's emails attached at the end of this review.
Biopharm	N/A			
ODS/DMEPA	Labeling consult		Acceptable for trade name Pending for container labels	Pending
Methods Validation	N/A	Date of this review	Acceptable	
EA	N/A	Date of this review	Acceptable	Dr. Raanan Bloom in OPS concluded in his

				5/4/10 e-mail that the EA categorical exclusion claim, as submitted in the 4/16/10 amendment, is appropriate.
Microbiology	Sterility assurance		Acceptable	

The Chemistry Review for NDA 201-023

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a chemistry, manufacturing, and controls (CMC) standpoint pending an "acceptable" recommendation from the microbiology review. The Office of Compliance has issued an overall "acceptable" recommendation for the application. The following comments should be included in the NDA action letter:

1. Based on the 12 months primary stability data, 6 month of accelerated data, and 36 months of the supportive stability data for drug substance and per ICH Q1E guidelines, an initial retest date of (b) (4) with storage at 5°C can be granted.

2. Based on the 12 months primary stability data, 6 month of accelerated data for drug product and diluent, and per ICH Q1E guidelines, an initial expiration dating period of 18-months for the drug product stored under the following conditions can be granted:

   - Store at 25°C (77°F); excursion permitted between 15°C – 30°C (59°F – 86°F)
   - Do not refrigerate.

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

Refer to the CMC PMRs to be conveyed to the applicant on June 2, 2010.

II. Summary of Chemistry Assessment

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

Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. The recommended dose of cabazitaxel is 25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks, in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment.

Drug Substance

Cabazitaxel (also referred as RPR116258 / XRP6258) is an antineoplastic agent belonging to the taxane class. (b) (4)

(b) (4) Cabazitaxel acetone solvate is a (b) (4) powder which is practically insoluble in water (b) (4) freely soluble in acetone and dichloromethane; and soluble in ethanol. Due to its extreme low solubility in aqueous solution, the cabazitaxel drug product is formulated in (b) (4) polysorbate 80.

(b) (4)

(b) (4)

(b) (4) The DMFs were reviewed by Dr. Brian Rogers. DMFs (b) (4) and (b) (4) have resolved their deficiencies and are adequate to support the NDA. DMF (b) (4) was reviewed previously by Chengyi Liang and found to be adequate to support a supplemental NDA. Clinical batches of drug substance were manufactured at Vitry France, which is also the same site used to manufacture the three primary stability batches and will be the commercial drug substance supplier.

Batch release data for the toxicology batches, early clinical batches, late clinical batches, primary stability batches and production batches were submitted. All tests conform to their criteria. During development, the following analytical methods were revised - HPLC for assay and related substances, GC for residual solvents, and microbial contamination test. Submitted data for the HPLC methods demonstrate that the updated HPLC method is comparable to the old HPLC method.

Controls for release and stability include testing for appearance, identification, assay, pH, color and clarity of the solution, purity, individual and total related substances, acetone content, residual solvents, (b) (4) heavy metals, water content and bacterial endotoxins. Organic impurities have either been qualified by toxicology studies or limited to the ICH Q3A recommended qualification threshold. Residual solvents are also controlled according to ICH Q3C guidelines except for acetone which is part of the solvate. Qualification of the specified impurities was consulted to the pharm/tox reviewer, , Dr. Sachia Khasar. With a few exceptions,

the applicant's claimed qualification levels have been found acceptable (refer to Dr. Khasar's emails attached at end of this review).

A genotoxic impurity, (b) (4), was identified in the Ames test. Test results for (b) (4) (b) (4) in the 3 primary stability batches and the 3 production batches show less than (b) (4) (b) (4) Safety evaluation of the observed levels of (b) (4) in the drug substance batches has been consulted to the pharm/tox reviewer. Based on Dr. Khasar's assessment, up to (b) (4) of (b) (4) in the drug substance is acceptable considering the patient population.

Stability studies were conducted at both long term (5ºC) and accelerated (25ºC/60% RH) storage conditions. Twelve months of long term and 6 months accelerated stability data from the 3 primary stability batches manufactured at the production scale using a process that is representative of the commercial process were submitted. All tests are within the proposed criteria. Overall, the drug substance appears to be stable under both long term and accelerated storage conditions. Photostability studies and other stress studies were conducted to characterize physical and chemical stability. Results show that drug substance is slightly photosensitive when exposed to intense light. Based on the available stability data and per ICH Q1E guidelines, an (b) (4) (b) (4) retest period for the drug substance stored under the refrigerated conditions (2–8°C) can be granted.

Drug Product

The drug product, JEVTANA (cabazitaxel) Injection, 60 mg/1.5 mL, is supplied as a non-aqueous concentrated solution for infusion co-packaged with a diluent vial containing 5.7 mL of a 13% w/w aqueous solution of alcohol (USP). The diluent is to be used for preparation of a premix solution of 10 mg/mL of cabazitaxel, followed by a second dilution of the appropriate dose in 0.9% sodium chloride solution or 5% dextrose solution in an infusion bag. Both concentrated drug solution and the diluent are each packaged in a 15 mL Type I clear glass vial closed with a grey (b) (4) rubber closure with a transparent (b) (4) (b) (4) and capped with an aluminum cap covered with a light green plastic flip-off cap. All formulation excipients comply with USP/NF compendial requirements.

Due to the (b) (4) of cabazitaxel acetone solvate in aqueous solution (b) (4) the drug product is formulated with a (b) (4) polysorbate 80. The overall drug product manufacturing process and formulation was unchanged during drug development and through commercialization. The commercial and clinical formulations differ in fill volume of the vials; 80 mg/2 mL for the clinical formulation and 60 mg/1.5 mL for the commercial formulation. Drug product is manufactured by Aventis Pharma in Dagenham, United Kingdom. The proposed commercial batch size is (b) (4) which will produce approximately (b) (4) (b) (4) The drug product manufacturing process is (b) (4)

In-use compatibility studies for the premix solution and infusion solution demonstrate suitable chemical stability of both solutions when stored under the ambient or refrigerated conditions.

Physical stability studies have demonstrated that both the premix solution and the infusion solution are (b) (4) which have a risk of crystallization when stored extensively, i.e. crystallization was observed in infusion solution stored at 30°C for 48 hours. The instruction in the package insert for the preparation and storage of the premix solution and the infusion solution includes cautionary statement and directions to avoid the potential crystallization situations. In addition, a proposed post-marketing requirement to study the physical stability has been conveyed to the applicant.

The drug product specification is typical for a small parenteral product for IV administration and includes testing for appearance, identification, pH, assay, degradation products, particulate matter, bacterial endotoxins, and sterility. Degradation products are limited to the ICH Q3B recommended qualification threshold and/or the maximum qualification levels of the toxicology studies (acceptance with concurrence of the pharm/tox reviewer, Dr. Khasar).

Primary stability studies were conducted at both long term (5ºC, 25ºC/60%RH, and 30ºC/65%RH) and accelerated (40ºC/75%RH) storage conditions on 3 registration batches manufactured at the intended commercial scale and site using the proposed commercial process, and packaged in the proposed commercial packaging system. Twelve months of long term (each condition) and 6 months of accelerated primary stability data are submitted. Based on the primary stability data generated on three commercial scale batches stored under the long term storage conditions (25°C/60% RH and 30°C/65 % RH) and per ICH Q1E guidelines, an 18 months shelf life can be grated. Long term stability data on the diluent vials also supports an initial 18 month shelf life. Since the drug product configuration is a two vial kit, the overall shelf life is based on the stability of both the drug concentrate vial and the diluent vial. Data from both vial products support an overall initial shelf life of 18 months when stored at the following condition:

25°C (77°F); excursion permitted between 15°C – 30°C (59°F – 86°F); Do not refrigerate.

CMC information for the diluent is also submitted in the drug product section. All excipients used to manufacture the diluent comply with USP compendial standards. The manufacturing process (b) (4) Appropriate release and stability testing are proposed with supporting batch data and stability data.

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

Drug product is an injectable dosage form supplied as a two vial configuration, a single use concentrated drug vial that contains 60 mg cabazitaxel in 1.5 mL of polysobate 80, and a diluent vial that contains 5.7 mL of 13% ethanol in Water for Injection.

The entire content of the diluent vial is to be withdrawn and added to the concentrated drug vial to obtain a premix solution containing approximately 10 mg/mL of cabazitaxel. Premix solution is prepared by repeated inversions for at least 45 seconds to assure complete mixing of the concentrated drug solution and the diluent. Immediately following preparation, a volume of

premix solution (calculated based on a dose of 25 mg/m^2) is withdrawn and to be injected into a PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. Concentration of the infusion solution should be between 0.10 mg/mL and 0.26 mg/mL. Diluted infusion solution should be used for intravenous administration immediately, or within 8 hours if stored at room temperature or within 24 hours if stored at refrigerated conditions (including the 1-hour infusion).

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint. There are no outstanding Chemistry, Manufacturing, and Controls issues.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao Hong Chen, Ph.D.
Branch Chief Name/Date: Sarah Pope Miksinski, Ph.D.

C. CC Block

Christy Cottrell/OODP/DODP/Regulatory PM
Haripada Sarker/ONDQA/PAL
Deborah Mesmer/ONDQA/PM
Mike Adams/ONDQA/Acting Branch Chief
Richard Lostritto/ONDQA/DNQA I Director
Sue Ching Lin/ONDQA/CMC Reviewer
Brian Rogers/ONDQA/CMC Reviewer

131 pages of chemistry Review has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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

/s/

XIAO H CHEN
06/02/2010

SUE CHING LIN
06/02/2010

BRIAN D ROGERS
06/02/2010

WILLIAM M ADAMS
06/02/2010
William Adams, acting for Sarah Pope Miksinski

Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	201-023 (for CMC, amendment 001 of 2/25/2010)
Applicant:	Sanofi-aventis U.S. Inc. on behalf of sanofi-aventis U.S. LLC27
Letter Date:	December 18, 2009
Stamp Date:	3/31/2010
PDUFA Goal Date:	9/30/2010 (priority – early action requested)
Tradename:	Not proposed
Established Name:	Cabazitaxel
Dosage Form/Strength:	Solution - 60 mg/1.5mL
Route of Administration:	IV
Indication:	Metastatic prostate cancer that progressed on or after docetaxel-based treatment.

Regulatory Filing	
Related IND	For 505 (b) (1) IND 56,999
Assessed by:	Haripada Sarker

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

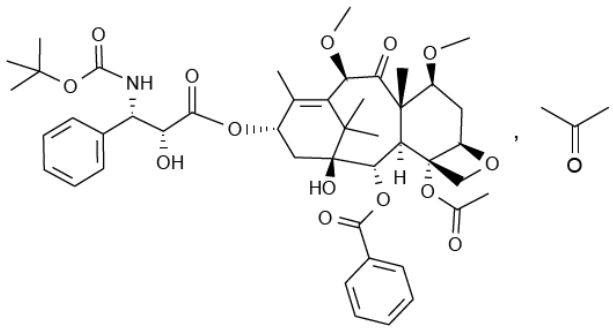
Background Summary
The drug cabazitaxel is a [redacted] (b) (4). The application introduces the drug product, cabazitaxel, which is supplied as 40mg/mL solution concentrate of one strength (60mg/1.5 mL as cabazitaxel acetone solvate) supplied in a vial. The product has to be reconstituted with the supplied diluent to make an injection concentrate, which is then reconstituted with 5% Dextrose injection or 0.9% Sodium Chloride Injection before administration.

In pre-NDA Type C meeting dated February 24, 2009, under IND 56,999, several CMC issues related to the drug substance (DS) starting material and in-use stability of the drug product (DP) infusion solution were discussed. The CMC information of the NDA is submitted in CTDQ format.

Drug Substance (DS)

(b) (4)

Cabazitaxel is an optically active compound. It is a semi-synthetic drug substance made from its (b) (4) (b) (4) Cabazitaxel is highly lipophilic and practically insoluble in water. As the structural formula of Cabazitaxel has multiple stereogenic centers, many isomers are theoretically possible. Cabazitaxel acetone solvate drug substance in solid form is very stable at room temperature. In solution, Cabazitaxel (b) (4) Two DS structurally related impurities are indicated in the submission. Genotoxic impurity (b) (4) is indicated during the DS synthesis. A request has been made to Office of Compliance to assess cGMP status for the DS related sites listed in the submission. The DS is identified with following structure:



Cabazitaxel acetone solvate

Applicant provided DS stability data for three registration batches covering the period of 12 months under long term storage condition (refrigerated, between 2°C and 8°C), and 6 months under accelerated storage at 25°C/60% RH. Based on the stability test data, the applicant proposes a retest period of (b) (4) when stored at refrigerated conditions, between 2°C and 8°C.

DS Critical Issues

- In solution, [redacted] formation of variety of isomers. Degradation products of cabazitaxel should be evaluated as per ICH Q3A (R).
- Justify why the limit of the genotoxic impurity, [redacted] should not be included in specification.
- EER information for DS needs to be re-examined for accuracy.
- A total of 5 Type II DMFs are cross-referenced for the intermediates [redacted] and [redacted] and the drug substance. DS and the intermediates are of [redacted] origins. Verify the in-house controls for intermediates [redacted] and [redacted] (specifically [redacted]) from different suppliers.
- The cross-referenced DMFs for DS information should be evaluated as per ICH Q3A (R) to support the NDA.
- Since [redacted], EA information is required to justify the claim.

Drug Product (DP)

The finished drug product is supplied as a solution concentrate with strength 60 mg/1.5 mL as cabazitaxel acetone solvate, which is co-packaged with a solvent vial containing [redacted] of a 13% w/w aqueous solution of alcohol (USP), also referred to as ethanol (96 per cent) in Ph. Eur., for preparation of an intermediate premix at 10 mg/mL, prior to dilution with 0.9% sodium chloride solution or 5% dextrose solution in an infusion bag.

Table 1. The composition details of cabazitaxel concentrate for solution for infusion, 60 mg/1.5 mL are provided in following.

Components	Composition per Unit	Function	Reference to standards [f]
Cabazitaxel acetone solvate [a]	60 mg	Active ingredient	In-house
Polysorbate 80 [redacted]	[redacted]	[redacted]	In-house (based on Ph.Eur., USP-NF, JP)
[redacted]	[redacted]	[redacted]	USP-NF, Ph.Eur., JP
[redacted]	[redacted]	[redacted]	USP-NF, Ph.Eur., JP

(a) : expressed as solvent-free and anhydrous drug substance.

[redacted]

(d) : USP standard term corresponding to ethanol anhydrous Ph.Eur.

[redacted]

(f) : When it is referred to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.

Note: A [redacted] overfilling is introduced to compensate for the losses during the preparation of the premix and the extractability of the dose from the premix. The target fill volume is [redacted] corresponding to target fill weight of [redacted]

Table 2. Solvent for dilution for cabazitaxel (below).

COMPONENTS	COMPOSITION		FUNCTION	REFERENCE TO STANDARDS [d]
	Percentage	Per Unit		
Alcohol [a]	13 % w/w [c]	(b) (4)		USP-NF, Ph. Eur.
Water for Injection q. s. [b]	100 %	(b) (4)		USP-NF, Ph. Eur., JP

(a): USP standard term corresponding to ethanol 96 % Ph. Eur.
(b): quantity sufficient for
(b) (4)
(d): When it is referred to a Pharmacopeia, this means that the current edition of this Pharmacopoeia is applied.

As cabazitaxel and docetaxel (Taxotere®) exhibit similar structures, it was verified that the Taxotere® two vial formulation (commercialized worldwide), which contained polysorbate 80 as surfactant, would be appropriate for cabazitaxel acetone solvate (following Table 3).

Table 3. Comparative cabazitaxel and docetaxel formulation

Components		Amount per Unit	Percentage formula	Function
Cabazitaxel concentrate (a)	Taxotere® concentrate (b)	80 mg/2 mL		
Cabazitaxel, acetone solvate	Docetaxel, trihydrate			Active substance
equivalent to solvent-free cabazitaxel	equivalent to anhydrous docetaxel	80 mg	(b) (4)	
Polysorbate 80	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)	(b) (4)
	(a)	-	-	

(a): Cabazitaxel initial presentation at 80 mg/2 mL.
(b): Taxotere two-vial formulation composition.
(b) (4)

Applicant utilizes the DP pharmaceutical development experiences of Docetaxel to develop cabazitaxel injection for this submission. The manufacturing and controls for cabazitaxel and docetaxel appears to be very similar.

The proposed DP manufacturing site is listed below:

Aventis Pharma, Dagenham
Rainham Road South
Dagenham
Essex RM10 7XS
UK

CMC information on solvent for dilution for cabazitaxel is provided.

Two different acceptance criteria for DP impurities are proposed for release and for stability specification as following. Also the unit “m/m” is not clear from the specification.

(b) (4)

Applicant indicated that specification excludes drug substance process impurities and those arising from excipient polysorbate 80.

Stability Summary for both Cabazitaxel concentrate (60mg/1.5mL) and solvent diluent (Table 2) are provided separately for long term and accelerated conditions as following Table 5. Long term stability data are provided for 12 months, both for DP concentrate and solvent.

Table 5. Stability Summary for both Cabazitaxel concentrate and solvent diluent

Batch number	Batch size	Packaging	Storage condition	Completed (and proposed test intervals)	Conclusion
Cabazitaxel concentrate					
DI-01567 D8C599 DI-01568 D8C600 DI-01569 D8C601	(b) (4) (b) (4)	15 mL, Type 1, clear glass vial closed with a (b) (4) rubber closure, (b) (4)-coated, sealed with an aluminium cap with plastic lid	**Accelerated** 40 ± 2°C / 75 ± 5 % RH	0, 1, 2, 3, 6	Complies with specification up to six months.
			Long Term 25 ± 2° C / 60 ± 5 % RH	0, 3, 6, 9, 12, (18, 24, 36)	Complies with specification up to s12 months, further study is ongoing.
Solvent for dilution for cabazitaxel					
DI-01572 DI-01573 DI-01574	(b) (4) (b) (4)	15 mL, Type 1, clear glass vial stoppered with a (b) (4) rubber closure coated with a transparent (b) (4) coating.	**Accelerated** 40 ± 2°C / 75 ± 5 % RH	0, 1, 2, 3, 6	Complies with specification up to six months.
			Long Term 25 ± 2° C / 60 ± 5 % RH	0, 3, 6, (9, 12, 18, 24, 36)	Complies with specification up to 12 months, further study is ongoing.

Supporting stability data are also provided under refrigerated conditions (5°C to 8°C). Appearance of the content of the drug product does not comply with a clear solution. It is not clear from the submission whether the precipitate is sourced from any impurities/degradants in DP. The 3 primary stability batches have shown a precipitate; however, the precipitates were demonstrated to re-dissolve after shaking. Stability data also provided for freeze-thaw cycle: 3 days at -20°C followed by 4 days at +30°C/65 % RH.

No statistical analysis is included to support the proposed DP expiration dating. The Applicant proposes a (b) (4) expiration dating period for the Cabazitaxel concentrate, when stored at 25°C (77°F); excursion permitted between 15°C – 30°C (59°F – 86°F) -Do not refrigerate.

CMC information is also provided for solvent for dilution of cabazitaxel. Shelf-life and storage conditions for solvent are proposed similar to those for the DP. However, no test data is available for stability data of DP co-packaged with solvent. Based on previous experience in other approved NDAs where similar co-packaged DPs are used, and no stability data are noted for co-packaged DP.

Drug Product Critical Issues

- New degradants in DP concentrate (finished dosage form) and infusion solution
- Check EES of DP sites for accuracy.
- DMFs for DS manufacturing and container/closure systems need to be reviewed for adequacy of the NDA.
- Two different acceptance criteria for DP impurities are proposed for release and for stability specification. These will need to be harmonized to reflect a single release and stability specification.
- Provide in-use stability and compatibility data for the drug product infusion solution over the period of intended storage time.
- Cabazitaxel concentrate shows a precipitate when stored under refrigerated conditions. Check the precipitate for any possibility of forming degradants, and confirm any impact on overall DP quality.
- Provide stability data (or justify) for the DP co-packaged with solvent (solvent for dilution for cabazitaxel).
- Justification of (b) (4) expiration based on 12-months stability data in the submission. Determine whether ICH Q1E can be applied for this extrapolation to justify the proposed expiration.

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Ref. 1.12.14 under regional information. EA is required and was requested on 4/7/10.
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		.

10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Review issue.
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √ √		**Microbiology** **Biopharm** Statistics (stability) OCP/CDRH/CBER LNC DMEPA **EER** **EA**

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LOA Included
(b) (4)	Sanofi Chimie 9 quai Jules Guesde 94403 Vitry-sur-Seine, France	XRP6258 cabazitaxel acetone	Yes
	Sanofi Chimie 9 quai Jules Guesde 94403 Vitry-sur-Seine, France	(b) (4)	Yes
		(b) (4)	Yes
			Yes
			Yes
			Yes
			Yes

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

Due to the complexity of the NDA, multiple reviewers are recommended. CMC comments will be sent to Applicant separately as IR.

Comments and Recommendations
Provided that the environmental assessment information below is adequately addressed, this application is fileable. Facilities have been entered into EES for inspection. Multiple reviewers may be needed due to the large number of DMFs associated with DS. No CMC comment in 74-day letter.

Haripada Sarker — May 19, 2010
CMC Lead — Date

William M. Adams, Ph.D. — May 19, 2010
Acting Branch Chief — Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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

/s/

HARIPADA SARKER
05/19/2010

WILLIAM M ADAMS
05/20/2010
William Adams acting for Sarah Pope Miksinski