

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203551Orig1s000

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 203551/000
 Approval Date: 14-MAR-2012
 Effective Date: 14-APR-2013

Action Goal:
 District Goal: 16-JUL-2012

Applicant: ACTAVIS INC
 1600 STEWART AVE
 WESTBURY, NY 11590

Brand Name: DOCETAXEL INJECTION
 Estab. Name:
 Generic Name:

Priority: 5
 Review Code: 150

Product Number; Dosage Form; Ingredient; Strengths
 001; SOLUTION, CONCENTRATE; DOCETAXEL; 20MG/1ML
 002; SOLUTION, CONCENTRATE; DOCETAXEL; 80MG/4ML
 003; SOLUTION, CONCENTRATE; DOCETAXEL; 140MG/7ML

Application Comment: 505(B)(2)
 FULL ESTABLISHMENT INFORMATION PROVIDED ON 3/23/12 (on 28-MAR-2012 by D. MESMER (HFD-800)
 3017964023)

Key Contacts:	D. MESMER	Project Manager	(HFD-800)	3017964023
	X. CHEN	Review Chemist		3017961337
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	ACCEPTABLE	on 08-JAN-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 02-JAN-2013	by EES_PROD		
	ACCEPTABLE	on 31-AUG-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 29-MAR-2012	by EES_PROD		

Printed on

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** FEI: 3003337238
S.C. SINDAN S.R.L
11TH ION MIHALACHE BLVD
BUCHAREST 1, , ROMANIA 011171

F No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Name: MANUFACTURES, TESTS, AND STABILITY TESTS DRUG PRODUCT
CFN Provided: CFN PROVIDED BY APPLICANT IS: 3005566806 (on 28-MAR-2012 by D. MESMER (HFD-800) 3017964023)
File: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
3MITTED TO OC	29-MAR-2012				MESMERD
3MITTED TO DO	30-MAR-2012	10-Day Letter			SMITHDE
RECOMMENDATION	31-MAR-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
RECOMMENDATION	02-APR-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE
3MITTED TO DO	02-JAN-2013	10-Day Letter			RAMANADHAMM
MAJOR AMMENDMENT RECEIVED ON 11/12/12. PDUFA CLOCK EXTENDED BY 3 MONTHS TO 4/14/13. REQUEST EXTENSION OF RE-EVALUATION DATE TO COVER CURRENT PDUFA					
RECOMMENDATION	02-JAN-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
AC THROUGH 5/6/2013 (+1MO) TO COVER THIS REVIEW CYCLE					
RECOMMENDATION	08-JAN-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

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

(b)(4)

F No:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment comment: MANUFACTURES DRUG SUBSTANCE, DOCETAXEL. APPLICANT PROVIDES THE FOLLOWING ADDRESS:

(b)(4)

(on 28-MAR-2012 by D. MESMER (HFD-800)

3017964023)

file: NON-STERILE API BY CHEMICAL SYNTHESIS

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
INSPECTION PERFORMED See EIR.	(b)(4)		(b)(4)		RORY.GEYER
COMMITTED TO OC					MESMERD
COMMITTED TO DO		GMP Inspection			SMITHDE
SIGNED INSPECTION TO IB		GMP Inspection			PHILPYE
DE EW					PHILPYE
RECOMMENDATION INSPECTION ENDING	(b)(4) CLASSIFIED VAI.			ACCEPTABLE INSPECTION	STOCKM
RECOMMENDATION	(b)(4)			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

NDA 203-551

Docetaxel Injection Concentrate

Actavis Inc.

Xiao-Hong Chen, Ph.D.

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

CMC Review of NDA 203-551

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

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Chemistry Review Data Sheet

1. NDA 203-551
2. REVIEW #1
3. REVIEW DATE: 13-February-2013
4. REVIEWERS: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 110,851	21-MAY-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	14-MAR-2012
Amendment	17-JUN-2012
Amendment	30-SEP-2012
Amendment	23-Oct-2012
Amendment	05-Nov-2012
Amendment	12-Nov-2012
Amendment	12-Nov-2012
Amendment	20-Nov-2012
Amendment	28-Nov-2012
Amendment	04-Dec-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Actavis Inc.

Chemistry Review Data Sheet

Address: 60 Columbia Road, Building B
Morristown, NJ 07960
Representative: Donald H. Chmielewski, Senior Associate
Lachman Consultant
Telephone: 908-659-2317

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Docetaxel
Code Name/# (ONDQA only): SPT1141
Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Breast, non-small cell lung, prostate, gastric adenocarcinoma, head and neck cancers

11. DOSAGE FORM: Concentrate for solution for infusion

12. STRENGTH/POTENCY: 20 mg/1 mL, 80 mg/4 mL, and 140 mg/7 mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

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

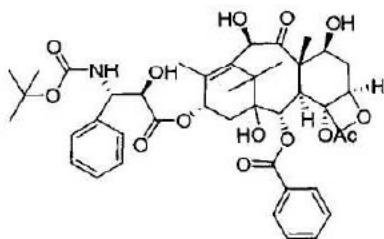
SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

(2R, 3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5beta, 20-epoxy-1,2 alpha, 4,7 beta, 10 beta, 13 alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate



Molecular formula: C₄₃H₅₃NO₁₄

Molecular weight: 807.88

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)	Manufacturer of the drug substance, Docetaxel	3	Adequate	10/20/2009	Reviewed by Debasis Ghosh, M
(b)(4)	III	(b)(4)	Glassware containers (b)(4)	3	Adequate	01/28/2011	Reviewed by Yong-de Lu in support of a CMC supplement of NDA.
(b)(4)	III	(b)(4)	Manufacturer of the stoppers and caps (b)(4)	1	Adequate	11/8/2012	Reviewed by Xiao-Hong Chen for this application.

*There was a typographical error in the spelling of (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")

Chemistry Review Data Sheet

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
NDA	20449	Sanofi	Sanofi's NDA is the subject of the RLD

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EES	Site inspections	21-Aug-2012	Acceptable	OC recommendation made on August 31, 2012
Pharm/Tox	DS and DP Impurity and excipient (Povidone)	17-Aug-2012	Acceptable	Consult through email. Refer to Dr. Wei Chen's email dated 20-Aug-2012 attached at the end of this review.
Biopharm	Review of biowaiver request made by Actavis.	24-Nov-2012	Acceptable	Reviewed by Dr. Elsbeth Chikhale.
ODS/DMEPA	Labeling review	13-Feb-2013	Acceptable	Reviewed by James Schlick, RPh, MBA.
Methods Validation	N/A	Date of this review	Acceptable	
EA	Environment Assessment	25-Oct-2012	Acceptable	Dr. Raanan Bloom found the claim for categorical exclusion Acceptable. Refer to his review dated Jan 14, 2013.
Microbiology	Sterility assurance	1-Nov-2012	Acceptable	Dr. Steven Donald recommended Approval in his review dated 17-Oct-2012.

The Chemistry Review for NDA 203-551

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA perspective the application is recommended for approval with an expiration dating period of 24 months for Docetaxel Injection Concentrate® (20 mg/mL, 80 mg/4 mL and 140 mg/7 mL) when stored at 25°C (77°F), protect from light. The following comment should be included in the NDA action letter:

Based on the primary stability data submitted the Agency grants a 24 months shelf life for the drug product stored under the following storage conditions:

Store at 25°C (77°F), Protect from light

B. Recommendation on Post-Marketing Requirements and/or Commitments, and/or Risk Management Steps, if Approvable

N/A.

II. Summary of Chemistry Assessment

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

Docetaxel Injection Concentrate is the subject of 505(b)2 NDA 203-551 submitted on 14-MAR-2012. Docetaxel is used in the treatment of the following kinds of neoplasm: breast cancer; non-small cell lung cancer; prostate cancer; gastric adenocarcinoma; head and neck cancer. This 505(b)2 NDA cross refers to the Reference Listed Drug (RLD), Taxotere NDA 020449 approved on May 14, 1996 for Sanofi Aventis US.

Drug Substance

Docetaxel is of the chemotherapy drug class taxane. Docetaxel is obtained by semi synthesis from 10-deacetylbaccatin III, a non-cytotoxic precursor extracted from needles of the European yew, *Taxus baccata*.

Docetaxel in anhydrous form is a white to almost-white microcrystalline powder with an empirical formula of $C_{43}H_{53}NO_{14}$ and a molecular weight of 807.9. Docetaxel trihydrate is a white to almost-white crystalline powder with an empirical formula of $C_{43}H_{53}NO_{14} \cdot 3H_2O$, and a molecular weight of 861.9. Docetaxel is very lipophilic and practically insoluble in water.

Executive Summary Section

Docetaxel exhibits cytotoxic activity on breast, colorectal, lung, ovarian, gastric, renal and prostate cancer cells. Docetaxel binds to microtubules reversibly with high affinity and has a maximum stoichiometry of 1 mole docetaxel per mole tubulin in microtubules. This binding stabilizes microtubules, and inhibits cell proliferation. Docetaxel is approximately twice as potent as paclitaxel in inhibiting cold and calcium-induced depolymerization of microtubules. It has also been found to lead to the phosphorylation of oncoprotein bcl-2, which is apoptosis blocking in its oncoprotein form.

A monograph for docetaxel trihydrate has been published in Ph.Eur. and USP. The solubility at 25°C (after 20.5 hrs) of docetaxel in various solvents was studied by the manufacturer, (b)(4). Docetaxel is freely soluble in ethanol and tetrahydrofuran; sparingly soluble in acetonitrile; soluble in solvents such as methanol, acetone, and ethyl acetate, and insoluble in n-hexane and water. Docetaxel is highly hygroscopic. The regulatory specifications for Docetaxel meet the current USP monograph for Docetaxel. Comparative testing for the proposed Docetaxel and RLD was conducted and the results demonstrate comparability between the two products.

Docetaxel drug substance is manufactured by (b)(4). Detailed Docetaxel drug substance manufacturing and controls information is provided in the Type II DMF (b)(4).

Drug Product

The drug product Docetaxel Injection Concentrate is a clear, oily, pale yellow solution with the following strengths: 20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL. The product is contained in either 5mL, 8mL or 11mL sterile (b)(4) colorless glass vials, and are closed with (b)(4) stoppers and sealed with aluminum seals with (b)(4) caps. The drug product is further diluted either in 0.9% Sodium Chloride or 5% Dextrose solutions prior to intravenous infusion. The inactive ingredients for the drug product consist of citric acid, povidone, polysorbate 80, and ethanol. All formulation excipients comply with USP/NF compendial requirements except (b)(4) that meets Ph. Eur.

Due to the extreme low solubility of docetaxel in water and other common vehicles used for the parenteral administration of drugs, the RLD Taxotere is formulated in the nonionic surfactant polysorbate 80 (b)(4). Organic solvents may dissolve docetaxel. However, when a water-miscible organics solvent containing docetaxel is diluted with aqueous infusion fluid, the drug may precipitate. Solubilization of docetaxel with surfactants such as polysorbate 80 allows for dilution of saturated or near saturated formulations of docetaxel. (b)(4)

Docetaxel Injection Concentrate is manufactured by using (b)(4) for parenteral drugs. Sterility assurance and manufacturing process validation are evaluated by the microbiology reviewer, Dr. Steven Donald. The microbiology reviewer has completed his review, and

Executive Summary Section

recommended approval from his perspective. Refer to Dr. Donald's microbiology review in Darfts dated 17-Oct-2012.

The proposed drug product specifications conform to the current USP monograph for Docetaxel. Non-compendial analytical methods have been validated. Batch analysis data for the nine production scale batches and one pilot batch were submitted and all results conform to the specifications.

Comparative impurity profile has been obtained by using the three pilot batches of Docetaxel 20mg/1mL, 80mg/4mL and 140mg/7mL after 6 months of storage under accelerated conditions (40°C/ 75%RH) and the Taxotere batches that are close to the expiry dates. The results demonstrate that they have similar impurity profiles. Due to the low solubility of docetaxel in aqueous solution, (b)(4)

A study was performed to compare the micelle size, size distribution and zeta potential, as well as micelle stability for the RLD and the proposed Docetaxel Injection Concentrate. The results showed comparable data except a slight increase of the CMC (Critical Micellar Concentration), which is not expected to influence the general solubility of the drug.

The stability studies were conducted under the long term (25°C/60%RH), intermediate (30°C/65%RH) and accelerated conditions (40°C/75% RH) and photostability as well as the in-use dilution conditions to support the proposed shelf life of 24 months. Based on 24 months long term and 12 months intermediate and 6 months accelerated stability data and photo stability data, a 24-month shelf life is granted for the drug product stored under the following conditions:

Store at 25°C (77°F), Protect from light.

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

The drug product Docetaxel Injection Concentrate 20 mg/mL (20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL) is intended for intravenous infusion. Unlike the RLD, Docetaxel injection concentrate requires no prior dilution with a diluent and is ready to add to the infusion solution (saline or D5W). The drug product is diluted in 250 mL of either in 0.9% Sodium Chloride or 5% Glucose Infusion solution to a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel injection concentrate is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel infusion solution is not exceeded.

Docetaxel injection infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be stored between 2°C and 25°C (36°F and 77°F) for 4 no more than hours. The docetaxel injection infusion solution should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

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

III. Administrative**A. Reviewer's Signature**

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao Hong Chen, Ph.D.

Acting Branch Chief Name/Date: Chidambaram Nallaperumal, Ph.D.

C. CC Block

Rajesh Venugopal/OODP/DODP/Regulatory PM

Haripada Sarker/ONDQA/CMC Lead

Deborah Mesmer/ONDQA/PM

Sarah Pope Miksinski/ONDQA/Acting Director ONNQA Division I

Elsbeth Chikhale/ONDQA/Biopharm Reviewer

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

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
02/22/2013

NALLAPERUM CHIDAMBARAM
02/22/2013
I concur.

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

OND Division: Division of Oncology Products 1
NDA: 203-551
Applicant: Actavis, Inc.
Letter Date: 14 March, 2012
Stamp Date: 14 March, 2012
PDUFA Goal Date: 14 January, 2013 (standard)
Tradename: Not proposed
Established Name: Docetaxel Injection Concentrate
Dosage Form/Strength: Solution Concentrate for Infusion - 20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL
Route of Administration: IV
Indication: Breast, non-small cell lung, prostate, gastric adenocarcinoma, head and neck.

Regulatory Filing For 505 (b) (2)
Related IND IND 110851 (RLD NDA 20-449)

Assessed by: Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

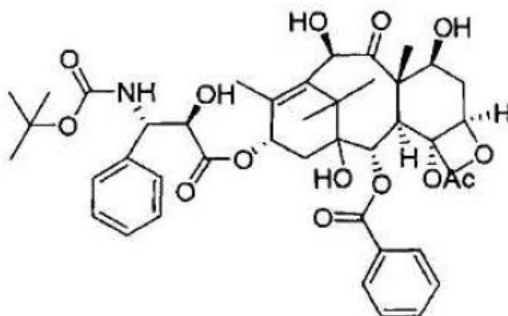
The application introduces the drug product, Docetaxel Injection which is supplied as 20mg/ml solution of three strengths. Docetaxel Injection is diluted with appropriate volumes of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to form the final dilution for infusion at a concentration of Docetaxel Anhydrous 0.3 mg to 0.74 mg/mL.

Applicant considered Taxotere® under NDA 20-449 as the reference listed drug (RLD), where the formulation is equivalent (40mg base/mL), except that a different excipient is used in the Actavis DP. Docetaxel (Taxotere) injection by Sanofi Aventis was previously approved by the agency 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.

The pre-NDA meeting package of this NDA was previously submitted to DOP2 under IND 110851. There were several CMC issues in pre-NDA meeting package. Agency sent the response, and requested the applicant to submit CMC information in the NDA (see draft meeting response in DARRTS dated 3/24/2011). After getting the preliminary response from the Agency, applicant cancelled the face-to-face meeting dated 3/24/2011. The CMC information of the NDA is submitted as per CTDQ format.

Drug Substance (DS)

Applicant refers to Type 2 DMF (b)(4) for all the DS CMC information. In this NDA, Actavis provided brief DS CMC information. Docetaxel is an optically active compound. It is a semi-synthetic drug substance made from natural precursor 10-deacetylbaccatin III. Docetaxel is highly lipophilic and practically insoluble in water. As the structural formula of docetaxel has multiple stereogenic centers, many isomers are theoretically possible. However, docetaxel drug substance in solid form is very stable. In solution, docetaxel is known to undergo pH assisted epimerization at C7, leading to the formation of 7-Epidocetaxel. Couple of DS structurally related impurities are indicated in the submission. Request has been made to office of compliance to provide inspection report for the DS related sites listed in the submission. The DS is identified with following structure.



DS will be manufactured by,
(b)(4)

Four batches of API ((b)(4)) manufactured by (b)(4) have been tested so far. Test data are provided including the justification of specification. Information on DS stability are cross-referred to DMF (b)(4). No QbD element is noted in the QOS so far.

DS Critical Issues

- In solution, docetaxel is known to undergo pH assisted epimerization, leading to the formation of variety of isomers. Degradation product of docetaxel should be evaluated, and may be compared with the specification for the DS in previously approved NDA 20-449.

- (b)(4) is the new DS manufacturer of Docetaxel from (b)(4). The cross-referred DMF (b)(4) for DS information should be evaluated to support the NDA. Specifically, any change in DS specification or stability in reference DMF (b)(4) when compared with previously approved RLD in NDA 20-449.
- Check the DS manufacturer information in EES for accuracy.
- Check for any QbD element in the DS section.

Drug Product (DP)

The finished drug product is a one vial formulation (solution concentrate). The drug product Docetaxel 20 mg/mL (20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL) is a solution concentrate for intravenous infusion. The drug product solution is further diluted either in 0.9% Sodium Chloride Infusion or 5% Glucose Infusion to produce a final dilution for IV infusion at a concentration of Docetaxel Anhydrous 0.3 mg/mL to 0.74 mg/mL. The drug product solution looks like a clear, oily, pale yellow solution.

Composition of the Drug Product (in mg/ mL and mg/ vial)

Components of the drug product	mg/ mL	Quantity (mg)/ vial			Role in formulation	Quality reference
		20mg/1mL	80mg/4mL	140mg/7mL		
Docetaxel	20.0	20.0	80.0	140.0	Active substance	Manufacturer Specification
Citric acid anhydrous	6.0	6.0	24.0	42.0	(b)(4)	Ph. Eur.
Povidone (Kollidon 12 PF)	100.0	100.0	400.0	700.0	(b)(4)	Ph. Eur.
Polisorbat80 (b)(4)	424.0	424.0	1696.0	2968.0	(b)(4)	Ph. Eur.
Ethanol (b)(4)	To 0.95 g/ 1.0 mL	To 0.95 g/ 1.0 mL ¹⁾	To 3.80 g/ 4.0 mL ²⁾	To 6.65 g/ 7.0 mL ³⁾	(b)(4)	Ph. Eur.
(b)(4)	-	-	-	-	(b)(4)	Ph. Eur.

NOTE: density of the solution: 0.950 g/mL (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Special Note: In above Table, Citric acid anhydrous and Povidone (Kollidon 12 PF) are additional components when compared to RLD.

In RLD (NDA 22-449), DP is a two-vial formulation (Injection Concentrate and Diluent) as following.

TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous solution.

TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE Injection Concentrate requires dilution with Diluent prior to addition to the infusion bag. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials.

A comparative composition between the RLD and the DP of this NDA is provided. Current NDA 201-551 is a one vial formulation whereas the RLD is a two vial formulation with concentration of 40mg/mL. In addition, two additional excipients, Citric acid anhydrous and Povidone (Kollidon 12 PF) are present in the current DP formulation. Applicant utilizes the DP pharmaceutical development experiences of RLD to develop Docetaxel injection for this submission. The manufacturing and controls for RLD and the DP appears to be very similar. The proposed manufacturing site is listed below:

S.C. SINDAN-PHARMA S.R.L.
11th Ion Mihalache Blvd.;
011171, Bucharest 1, Romania

Test data on 3 pilot batches (1 batch of each presentation form) and 4 industrial batches (commercial batches) of drug product (1 batch of 20 mg/ 1 mL; and 3 batches of 80 mg/ 4 mL) have been tested in order to check the compliance of the drug product with the proposed Quality Specification at Batch Release. All the batches appear to comply with the proposed specification.

The DP container closure system consists of the following component parts:

- (b)(4) Colourless glass vials, 5 mL, 8 mL and 11 mL - filling capacity;
- (b)(4) Rubber stoppers, for closing the vials with parenteral solutions, (b)(4) type;
- Metallic aluminium caps with (b)(4) disk.

Specifications for all the DP strengths (20 mg/1 mL, 80 mg/4 mL, 140 mg/7 mL) are provided both at release and at stabilities. The acceptance criteria for DP impurities are proposed for release and for stability specification appears to be same. Stability profiles for both Docetaxel concentrate and infusion solution are provided for long term and accelerated conditions as following.

DP stability testing program includes three pilot batches (one per strength) and 4 industrial batches (one batch of 20mg/1mL and three of 80mg/4mL) as per ICH Q1E. Stability test data are provided with the following testing periods and conditions:

- 6 months under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5^{\circ}\text{C}$);
- 12-36 months under intermediate conditions ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5^{\circ}\text{C}$);
- 12-36 months on long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5^{\circ}\text{C}$).

No significant changes have been recorded during stability testing, regardless the storage conditions, with regard to the following tested parameters: appearance, colour, clarity, visible particles, subvisible particles, water content.

Type of performed studies

- Drug Product Photo-stability Study
- Drug Product Stability Study as packaged for sales
- Drug Product Stability Study after dilution

Drug product after dilution

The purpose of the study was to evaluate the physico-chemical stability of the diluted solution 0.74 mg docetaxel/ mL with 0.9% NaCl solution for infusion and 5% Glucose solution for infusion when kept at about 25°C and light exposure (simulating in-use conditions).

No significant differences (no significant assay decrease; no significant increase in impurities levels) have been recorded in chemical stability of the diluted solutions regardless the used solution for infusion or the storage material. The diluted solutions are chemically stable for the tested period (8h ours or 24 hours). However, there is an occurrence of precipitation (physical instability) of the diluted solutions observed, which is assumed to be related to the storage material (precipitation occurs more often when PVC bags are used) and to the way the diluted solution is prepared. Applicant indicated that when the diluted solution is prepared using 10 vials of the lowest strength 20mg/1mL, diluted solutions tend to precipitate due to the repeated maneuvers involved when volumes of about 1mL solution are extracted from the vials and introduced into infusion bottle/ bag. A longer physical stability of the diluted solutions have been noticed when they have been prepared using 2 vials of the highest strength of 140mg/7mL.

No statistical analysis is included to support the proposed DP expiration dating. The Applicant proposes a 24-month expiration dating period for the Docetaxel concentrate, when stored 25°C ($\pm 2^\circ\text{C}$) / 60% ($\pm 5\%$) RH in absence of light.

The physico-chemical stability of the drug product after dilution (0.74mg/mL) in the recommended solutions for infusion (0.9% NaCl and 5% glucose) has been demonstrated for 8 hours at about 25°C, and light exposure.

No QbD element is noted in the QOS so far in the DP section.

Drug Product Critical Issues

- New degradants in DP concentrate (finished dosage form) and infusion solution, when compared with RLD specification.
- Check EES of DP sites for accuracy.
- DMFs for DS manufacturing and container/closure systems need to be reviewed for adequacy of the NDA.
- Occurrence of precipitation (physical instability) of the diluted solutions observed in PVC bag.
- Justification of 24-months DP shelf-life.
- The DP labeling, which is submitted in PRL format, need to be evaluated for its relevant CMC sections.
- Check for any QbD element in the DP section.\
- Confirm acceptability of the proposed dosage form (Concentrate). This will probably need revision during the review clock.

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 <u>street</u> 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?	√		
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 Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMETPA EER

Have all DMF References been identified? Yes (√) No (0)

DMF Number	Holder	Description	LOA Included
(b)(4) (Type II)	(b)(4)	Manufacturer of the drug substance, Docetaxel	Yes
(b)(4) (Type III)	(b)(4)	Provided LoA for Vial Manufacturers 5, 8 and 11mL vials	Yes
(b)(4) (Type V)	(b)(4)	Stopper Manufacturer Rubber stopper, (b)(4)	Yes

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker
Pharmaceutical Assessment Lead (PAL)

April 18, 2012
Date

Sarah Pope Miksinski, Ph.D.
Branch Chief

April 18, 2012
Date

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
04/18/2012

SARAH P MIKSINSKI
04/20/2012