CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-312

Docetaxel Injection

Apotex, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Reference ID: 3052037

Table of Contents

Reference ID: 3052037

CMC Review Data Sheet

1. NDA 22-312

2. REVIEW #: 5

3. REVIEW DATE: 23-NOV-2011

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	03-Mar-2008
Correspondence (C)	27-MAR-2009
Amendment # 3 (BC)	17-Sept-2008
Amendment #4 (AC)	3-Dec-2008
Amendment # 5 (BC)	5-March-009
Amendment # 7 (BC)	12-March-2009
Amendment (BC) Response to 12-JAN-2009 Letter	31-MAR-2009
Amendment (BL)	29-JUL-2009
Amendment (QR) – Response to 28-APR-2009 Letter	29-JUL-2009
Amendment (NR)	14-AUG-2009
Amendment (QR) Tel. Request.	10-SEP-2009
Amendment (b) (4) for Docetaxel Diluent	24-NOV-2009
Amendment – Withdraw an Alternate Analytical Testing Site (b) (4)	14-JAN-2010
Amendment – Response to C/R Letter dated 29-JAN-2010 and Revised Labeling	24-MAR-2010
Amendment – Response to Request for Information Letter dated 21-APR-2010	23-APR-2010
Amendment – Response for IR dated 28-APR-2010	29-APR-2010
Amendment – Labeling Amendment	04-JUN-2010
Amendment – Labeling Amendment	17-JUN-2010
Amendment – Micro.	23-JUL-2010
Amendment – Patent and Revised Labeling	05-AUG-2010
Amendment - (b) (4) Protocol	12-AUG-2010
Amendment – Withdraw (b) (4) Protocol	31-AUG-2010
Amendment - Patent	01-OCT-2010
Amendment – Patent	13-OCT-2010
Amendment – Response to C/R Letter dated 22-SEP-2010 Quality & Labeling	12-NOV-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to Information Request Letter	12-AUG-2011
Response to Complete Response Letter dated 04-MAY-2011	12-JUL-2011
Amendment - Labeling	03-MAY-2011
AMD – Correct Comparison Table between the Equipment and Manufacturing/Packaging Process (b) (4)	27-JAN-2011
Amendment CMC Information	10-DEC-2010

Reference ID: 3052037

Labeling Amendment – Response Information Request dated 03-OCT-2011	13-OCT-2011
Labeling Amendment – Response Information Request dated 24-OCT-2011	03-NOV-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex, Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada, M9L1T9
Representative:	Kiran Krishnan
Telephone:	954-384-3986

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: Concentrate : 40 mg/mL (20 mg/0.5mL and 80mg/2mL)
Diluent: For 20 mg size – 1.8 mL and
For 80 mg size – 7.1 mL

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: __Y__Rx ___OTC

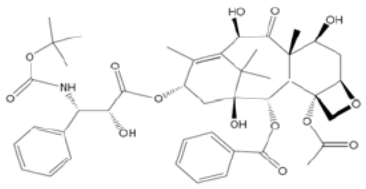
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

Reference ID: 3052037

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: 2aR-(2aα, 4β, 4aβ, 6β, 9α, (αR*, βS*), 11α, 12α, 12aα,12bα)]- β-[[(1, 1-dimethylethoxy)carbonyl]amino]- α-hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)- 2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12bdodecahydro-4, 6, 11-trehydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl]ester

Molecular Structure:



Molecular Formula: $C_{43}H_{53}NO_{14}$ Molecular Weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel anhydrous drug substance	1	Adequate	30-NOV-2009	See DMF review by J.Jee
	III		(b) (4)	1	Adequate	22-SEP-2003	By David Lewis
	V			1	Adequate	04-APR-2008	By John Arigo
	III			1	Adequate	22-APR-2009	By Sharmista Chatterjee
	V			1	Adequate	12-JUN-2009	By J. Wells

[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)

Reference ID: 3052037

B. Other Documents: NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ COMMENTS
Biometrics	N/A		No statistical analysis of drug product stability data deemed necessary.
EES	Acceptable	22-AUG-2011	D. Smith and A. Inyard
Pharm/Tox	Approvable	11-December-2009	Refer to final P/T review by M. Brower.
Biopharm	Acceptable	26-APR-2011	A. Dorantes
LNC	N/A		
Methods Validation	N/A		Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Categorical exclusion (see review)		See Review #1. S. Chatterjee
Microbiology	Approvable pending revision – deficiencies noted	Pending	S. Langille
DMEPA	Acceptable	26-JAN-2010	J. Schlick  RE NDA 22-312.msg

Reference ID: 3052037

The CMC Review for NDA 22-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval, pending on acceptable microbiology review and acceptable final carton and container labels. An acceptable OC recommendation was received on 22-AUG-2011. The container and carton labels were revised according to DMEPA recommendations, see CMC Review dated 17-MAR-2011 and DMEPA Review dated 05-APR-2011.

Based on the stability data provided, a 24-month expiration dating period is granted for the drug product when stored at controlled room temperature, 20°C to 25°C (59°F to 86°F), excursions permitted from 15°C to 30°C (68°F to 77°F) [See USP Controlled Room Temperature].

.

This review covers Amendment dated 12-JUL-2011 in response to C/R dated 04-MAY-2011. In addition, the following amendments were submitted late in the previous review cycle and were not reviewed in the previous review cycle:

1. *Amendment dated 10-DEC-2010 (reviewed this cycle):*

   a. Provides update Docetaxel Drug Substance, and (b) (4) specifications to comply with USP.
      - Docetaxel drug substance and (b) (4) specifications are updated to comply with the current USP.

   b. Provides update stability data for scale-up batch of the concentrate and for the diluent.
      - The 18 M updated stability data for scale-up batches of the Docetaxel Injection (Concentrate) and Docetaxel Injection (Diluent) is acceptable. The applicant proposed 24M expiry date. Based on Guidance for Industry, ICH Q1E Evaluation of Stability Data." A 24 M exp. date can be granted.

Reference ID: 3052037

c. Provides an updated method validation report for the DS assay, ID, and related compounds method (DOCE-DS-CB-90-RH).

- The updated method validation report for the DS assay, ID, and related compounds method (DOCE-DS-CB-90-RH) is acceptable.

d. Provides the addition of (b) (4) as an alternate testing site for sterility of the drug product concentrate and diluent.

2. *Amendment dated 27-JAN-2011 (reviewed this cycle)* – Correct Comparison Table between the Equipment and Manufacturing/Packaging Process (b) (4)

- The updated manufacturing equipment and packaging process from a CMC perspective is acceptable. However, further evaluation from Microbiology is pending.

3. *Amendment dated 03-MAY-2011(reviewed this cycle)* – Labeling

- All issues of carton, container and package insert labeling are satisfactorily revised. The only pending issue is adding the Lot. No. and Exp. Date as part of the container and carton labels.

4. *Amendment dated 12-JUL-2011 (reviewed this cycle)*– Responses to C/R dated 04-MAY-2011.

- All facilities used in the manufacturing of Docetaxel Injection (Concentrate) and Docetaxel Injection (Diluent) are acceptable by the Office of Compliance on 22-AUG-2011.

5. *Amendment dated 13-OCT-2011 (reviewed this cycle)* – Response to IR Letter dated 13-OCT-2011

- The revised carton and container labels submitted on 13-OCT-2011 reflect the recommended changes and they are acceptable by DMETS. However, the Lot. No. and the Exp. Date are not printed in the mock up carton and container labels. A comment to the sponsor was requested and was sent on 22-NOV-2011 to Apotex.

6. *Amendment dated 03-NOV-2011 (reviewed this cycle)* – Response to IR Letter (labeling comments) dated 24-OCT-2011.

   - The labeling submitted in the 04-NOV-2011 is acceptable to CMC.

B. 3. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments (See CMC review #1)

A. Description of the Drug Product(s) and Drug Substance(s)
See Review dated 17-MAR-2011.

B. Recommendation and Conclusion on Approvability
Based on IA, this NDA is recommended for approval from a CMC perspective, pending on acceptable microbiology evaluation and acceptable revised carton and container labels (adding Lot No. and exp. date).

C. Description of How the Drug Product is Intended to be Used
See Review dated 17-MAR-2011.

D. Basis for Approvability or Not-Approval Recommendation
The application is recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective, pending final acceptable container and carton labeling submission and an acceptable microbiology review.

III. Administrative

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary. It includes two drug product sections: one for the concentrate and another for the diluent.

A. Reviewer's Signature
See electronic signatures in DARRTS

B. Endorsement Block
See electronic signatures in DARRTS

C. CC Block
See DARRTS

27 Page(s) have 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/

JOSEPHINE M JEE
11/30/2011

SARAH P MIKSINSKI
12/02/2011

HARIPADA SARKER
12/02/2011

NDA 22-312

Docetaxel Injection

Apotex, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Reference ID: 2936935

Table of Contents

Reference ID: 2936935

Reference ID: 2936935

CMC Review Data Sheet

1. NDA 22-312

2. REVIEW #: 4

3. REVIEW DATE: 17-MAR-2011

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	03-Mar-2008
Correspondence (C)	27-MAR-2009
Amendment # 3 (BC)	17-Sept-2008
Amendment #4 (AC)	3-Dec-2008
Amendment # 5 (BC)	5-March-009
Amendment # 7 (BC)	12-March-2009
Amendment (BC) Response to 12-JAN-2009 Letter	31-MAR-2009
Amendment (BL)	29-JUL-2009
Amendment (QR) – Response to 28-APR-2009 Letter	29-JUL-2009
Amendment (NR)	14-AUG-2009
Amendment (QR) Tel. Request.	10-SEP-2009
Amendment (b) (4) for Docetaxel Diluent	24-NOV-2009
Amendment – Withdraw an Alternate Analytical Testing Site (b) (4)	14-JAN-2010
Amendment – Response to C/R Letter dated 29-JAN-2010 and Revised Labeling	24-MAR-2010
Amendment – Response to Request for Information Letter dated 21-APR-2010	23-APR-2010
Amendment – Response for IR dated 28-APR-2010	29-APR-2010
Amendment – Labeling Amendment	04-JUN-2010
Amendment – Labeling Amendment	17-JUN-2010
Amendment – Micro.	23-JUL-2010
Amendment – Patent and Revised Labeling	05-AUG-2010
Amendment - (b) (4) Protocol	12-AUG-2010
Amendment – Withdraw (b) (4) Protocol	31-AUG-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment - Patent	01-OCT-2010
Amendment – Patent	13-OCT-2010
Amendment – Response to C/R Letter dated 22-SEP-2010 Quality & Labeling	12-NOV-2010

Reference ID: 2936935

CMC Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex, Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada, M9L1T9
Representative:	Kiran Krishnan
Telephone:	954-384-3986

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: Concentrate : 40 mg/mL (20 mg/0.5mL and 80mg/2mL)
Diluent: For 20 mg size – 1.8 mL and
For 80 mg size – 7.1 mL

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: __Y__Rx ___OTC

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

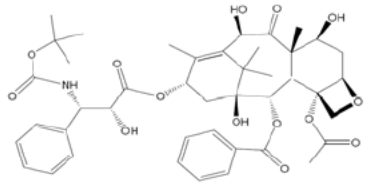
___X__Not a SPOTS product

Reference ID: 2936935

CMC Assessment Section

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: 2aR-(2aα, 4β, 4aβ, 6β, 9α, (αR*, βS*), 11α, 12α, 12aα,12bα)]- β-[[(1, 1-dimethylethoxy)carbonyl]amino]- α-hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)- 2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12bdodecahydro-4, 6, 11-trehydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl]ester

Molecular Structure:



Molecular Formula: $C_{43}H_{53}NO_{14}$ Molecular Weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel anhydrous drug substance	1	Adequate	30-NOV-2009	See DMF review by J.Jee
	III		(b) (4)	1	Adequate	22-SEP-2003	By David Lewis
	V			1	Adequate	04-APR-2008	By John Arigo
	III			1	Adequate	22-APR-2009	By Sharmista Chatterjee
	V			1	Adequate	12-JUN-2009	By J. Wells

[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)

B. Other Documents: NA

Reference ID: 2936935

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ COMMENTS
Biometrics	N/A		No statistical analysis of drug product stability data deemed necessary.
EES	Withhold	11 MAR 2011	Withhold
Pharm/Tox	Approvable	11-December-2009	Refer to final P/T review by M. Brower.
Clinpharm	Acceptable	12-February-2009	Refer to review by Jeanne Fourie.
LNC	N/A		
Methods Validation	N/A		Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Categorical exclusion (see review)		See Review #1.
Microbiology	Approvable pending revision – deficiencies noted	08-JAN-2010 and 01-SEP-2010	Refer to review by S. Langille. Await review for the comparability protocol submitted in Amendment dated 24-NOV-2009
DMEPA	Additional areas for improvements are identified.	26-JAN-2010	Refer to the 26-JAN-2010 Label and Labeling Review by Loretta Holmes. Applicant has addressed the issues cited in the C/R dated 28-APR-2009. Additional areas are identified in submission dated 29-JUL-2009.

Reference ID: 2936935

The CMC Review for NDA 22-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective until an acceptable OC recommendation is received. A withhold overall recommendation dated 11-MAR-2011 was issued by the Office of Compliance. GMP status of the manufacturing and controls facilities are as follows:

1. Apotex, 4100 Weston Rd., Signet Campus, Toronto, Canada – Withhold on 10-MAR-2011
2. Apotex, 3701 Weston Road, Toronto, Canada – Withhold on 10-MAR-2011
3. Apotex, 380 Elgin Mills Road, Richmond Hill, Ontario, Canada – Acceptable on 19-JAN-2011

(b) (4)

Include the standard language for lack of cGMP compliance in the action letter.

NOTE: This review cycle covered Amendment dated 12-NOV-2010.
Apotex submitted two Gratuitous Amendments dated 10-DEC-2010 and 27-JAN-2011, respectively. They were not reviewed in this cycle.

B. 3. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments (See CMC review #1)

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

(1) Drug Substance

Reference ID: 2936935

Docetaxel anhydrous is a white to off white crystalline powder. (b) (4) The anhydrous form of docetaxel is being used in this product. This form is practically insoluble in water, it is slightly soluble in chloroform and highly soluble in methanol, ethanol and acetone.

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 (b) (4) that is routinely monitored in the drug product.

Manufacturing information is provided in the DMF (b) (4)

For testing of the drug substance, apart from the tests reported in the Certificate Of Analysis (COA) by the manufacturer (b) (4) the sponsor has developed an in-house GC based method to confirm presence of residual solvents and an in-house HPLC based method to confirm detection in-organic impurities and assay. All acceptance criteria set were in accordance with ICH guidances. Batch data for two lots of drug substance that were used to manufacture the pilot stability drug product lots is provided in the NDA.

Docetaxel anhydrous is hygroscopic in high humidity. It is thus packed in (b) (4) It is to be stored protected from light in the suggested packaging configuration at 20 to 25ºC, and a retest period of (b) (4) is proposed. The DMF was found adequate (See J.Jee Review dated 30-NOV-2009).

(2) Drug Product

The drug product is available as 40 mg/mL concentrate solution of Docetaxel Anhydrous (API) in Polyethylene Glycol 300 NF (PEG-300) for Injection. This NDA is filed as a 505b(2) submission. The drug product is pharmaceutically equivalent to the Reference Listed Drug (RLD), Taxotere for injection (NDA 20-449) marketed by Sanofi Aventis. For this NDA, the sponsor developed docetaxel injection at the same therapeutic concentration as Taxotere in the infusion solution but with a different qualitative and quantitative formulation as compared to the RLD for both the injection concentrate as well as the diluent. The sponsor has not proposed any trade name for this product and does not intend to do so.

For this application, the sponsor requested a biowaiver in accordance with 21 CFR 320.22(b)(1). Their rationale is that since this is an intravenously administered product, the difference in excipient composition between the final dilution for injection between this product and the RLD would be self evident, and is not expected to have any impact on the safety and efficacy of the drug. This reviewer is in concurrence with this opinion since the starting dose is the same for both Apotex's product and the RLD. Furthermore, at the pre NDA meeting on September 26, 2007 for IND 78,376, the agency had communicated to the sponsor that a clinical study in support of this application is not required.

In the same fashion as the RLD, docetaxel injection is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of Docetaxel Anhydrous. In this case, the sponsor chose Polyethylene Glycol (PEG) 300 in place of Polysorbate 80, as in the RLD for

the injection concentrate. The injection concentrate also requires dilution prior to use. It is diluted by adding to it the entire withdrawable content of the accompanying diluent vial. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. This initial diluted solution (at a concentration of Docetaxel Anhydrous 10 mg/mL) is further diluted with an appropriate volume of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to produce a final dilution for IV infusion at a concentration of 0.3 mg/mL to 0.74 mg/mL Docetaxel. All utilized excipients are compendial grade.

The choice of manufacturing process for both the injection concentrate as well as the diluent was made on the basis of prior experience. The injection concentrate is manufactured at a (b) (4) The sponsor provided scale-up information of the injection concentrate (b) (4) as a major amendment dated March 29, 2009 and was reviewed in this cycle; microbiology recommended approval. Bulks for both the concentrate as well as the diluent are to be stored between 20-25ºC, protected from light. Amendment 29-JUL-2009 was a complete response to the FDA Action Letter dated 28-APR-2009, and amendment dated 24-NOV-2009 was submitted to propose (b) (4) for the Docetaxel Diluent, specifically (b) (4) at the Richmond Hill facility. The information provided in the 24-NOV-2009 amendment does not have any CMC issues and the Microbiology Review dated 17-SEP-2010 recommended approval. However, the Richmond Hill facility is deemed unacceptable by the Office of Compliance.

The injection concentrate specifications include quality tests for appearance, identity, assay, degradation products, and microbiology. In the original submission, it was noted that the specifications for release were (b) (4) the sponsor proposed the same set of specifications for both release and stability. It is noted from the specifications that four of the impurities are above the ICH Q3B(R2) limit of 0.2% and would thus have to be qualified. These are: (b) (4) In addition, it is not clear from the March 12, 2009 amendment whether the impurity (b) (4) is at all present in the product and if so at what levels. Pharmacology/Toxicology review concluded that the proposed limits are acceptable for safety. Please refer to the Pharmacology/Toxicology review for further details regarding impurity qualification (refer review by M. Brower dated 21-April, 2009).

Docetaxel Injection (b) (4) 20 mg/0.5 mL is packaged in 5 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover, while 80 mg/2 mL is packaged in 10 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover.

The diluent that is supplied with the injection concentrate contains polysorbate 80, NF and alcohol (b) (4), USP (Ethyl Alcohol) in Water for Injection, USP/EP.. Polysorbate 80 is used as a (b) (4) The RLD's diluent on the other hand is composed entirely of ethyl alcohol.

The current NDA submission also included a proposed (b) (4) protocol submitted on 29-JUL-2009. This protocol allowed for the (b) (4)

Reference ID: 2936935

(b) (4) (b) (4) This protocol was reviewed by Microbiology (see Reviews dated 08-JAN-2010 and 01-SEP-2010) and recommended that it was not acceptable. Apotex withdrew this (b) (4) protocol on 31-AUG-2010. (b) (4) the comparability protocol submitted on 24-NOV-2009 Amendment was reviewed by Microbiology on 17-SEP-2010 and recommended approval.

Amendment dated 24-MAR-2010 provided response to Complete Response Letter dated 29-JAN-2010, CMC Microbiology recommended approval on 17-SEP-2010.

On evaluation of the stability data, it was decided to grant the sponsor only 18 months of expiration, if the application were to be approved at this time. (b) (4) In addition, granting the 18 month expiration per the 18 month data provided is in accordance with ICH guidance Q1E, which states that no extrapolation be allowed if significant changes are observed during storage.

The submitted labels and labeling have been reviewed for this submission by Division of Medicine Error Prevention and Analysis (DMEPA). Several deficiencies, identified in their 27-FEB-2009 Review, were sent in the 28-APR-2009 Complete Response Letter. Apotex submitted their revisions on 29-JUL-2009. The revised carton and container labels were reviewed on 26-JAN-2010 by the DMEPA and this review concluded that the applicant have addressed all their comments; however, DMEPA have identified additional areas that need improvement and should be changed prior to approval; see comments sent to applicant, Executive Summary, I A Recommendation and Conclusion on Approvability. Apotex attempted to address these labeling issues in their 12-NOV-2010 Amendment; as of this review, we await for DMEPA recommendations.

The overall recommendation dated 10-MAR-2011 from the Office of Compliance is "Withhold"; For the proposed sites, Apotex facilities at Signet Campus, Toronto, Canada; and 3701 Weston Road, Toronto, Canada for the manufacturing and control of the drug product. Further, on 16-MAR-2011, the District recommendation for both sites is "Withhold"; see Attachment A.

B. Recommendation and Conclusion on Approvability

This application is not recommended for approval, see comment under II D

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

Docetaxel Injection is a microtubule inhibitor used for:
Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

This drug is administered intravenously over 1 hour every 3 weeks in patients pre-medicated with oral corticosteroids.

D. Basis for Approvability or Not-Approval Recommendation

The application cannot be recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective until acceptable container/carton and PI labeling are submitted. Also note that a withhold overall recommendation dated 10-MAR-2011 was issued by the Office of Compliance. Further, on 16-MAR-2011, the District recommendation for the proposed sites, Apotex facilities at Signet Campus, Toronto, Canada; and 3701 Weston Road, Toronto, Canada for the manufacturing and control of the drug product is "Withhold"; see Attachment A. Satisfactory resolution of these deficiencies is required before this application may be approved.

III. Administrative

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary. It includes two drug product sections: one for the concentrate and another for the diluent.

CC Block: entered electronically in DARRTS

11 Page(s) have been Withheld in full as b4 (CCI/TS) immediately following this page

Reference ID: 2936935

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
04/21/2011

SARAH P MIKSINSKI
04/21/2011

HARIPADA SARKER
04/21/2011

NDA 22-312

Docetaxel Injection

Apotex, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 22-312

2. REVIEW #: 3

3. REVIEW DATE: 17-SEP-2010

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	03-Mar-2008
Correspondence (C)	27-MAR-2009
Amendment # 3 (BC)	17-Sept-2008
Amendment #4 (AC)	3-Dec-2008
Amendment # 5 (BC)	5-March-009
Amendment # 7 (BC)	12-March-2009
Amendment (BC) Response to 12-JAN-2009 Letter	31-MAR-2009
Amendment (BL)	29-JUL-2009
Amendment (QR) – Response to 28-APR-2009 Letter	29-JUL-2009
Amendment (NR)	14-AUG-2009
Amendment (QR) Tel. Request.	10-SEP-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment [redacted] (b) (4) for Docetaxel Diluent	24-NOV-2009
Amendment – Withdraw an Alternate Analytical Testing Site [redacted] (b) (4)	14-JAN-2010
Amendment – Response to C/R Letter dated 29-JAN-2010 and Revised Labeling	24-MAR-2010
Amendment – Response to Request for Information Letter dated 21-APR-2010	23-APR-2010
Amendment – Response for IR dated 28-APR-2010	29-APR-2010
Amendment – Labeling Amendment	04-JUN-2010
Amendment – Labeling Amendment	17-JUN-2010
Amendment – Micro.	23-JUL-2010
Amendment – Patent and Revised Labeling	05-AUG-2010
Amendment - [redacted] (b) (4) Protocol	12-AUG-2010
Amendment – Withdraw [redacted] (b) (4) Protocol	31-AUG-2010

CMC Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex, Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada, M9L1T9
Representative:	Kiran Krishnan
Telephone:	954-384-3986

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: Concentrate : 40 mg/mL (20 mg/0.5mL and 80mg/2mL)
Diluent: For 20 mg size – 1.8 mL and
For 80 mg size – 7.1 mL

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: ✔ Rx ___ OTC

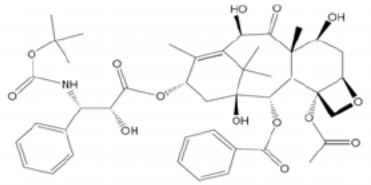
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

X Not a SPOTS product

CMC Assessment Section

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical Name: 2aR-(2aα, 4β, 4aβ, 6β, 9α, (αR*, βS*), 11α, 12α, 12aα,12bα)]- β-[[(1, 1-dimethylethoxy)carbonyl]amino]- α-hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)- 2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12bdodecahydro-4, 6, 11-trehydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl]ester

Molecular Structure:



Molecular Formula: $C_{43}H_{53}NO_{14}$ Molecular Weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel anhydrous drug substance	1	Adequate	30-NOV-2009	See DMF review by J.Jee
	III		(b) (4)	1	Adequate	22-SEP-2003	By David Lewis
	V			1	Adequate	04-APR-2008	By John Arigo
	III			1	Adequate	22-APR-2009	By Sharmista Chatterjee
	V			1	Adequate	12-JUN-2009	By J. Wells

[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)

B. Other Documents: NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ COMMENTS
Biometrics	N/A		No statistical analysis of drug product stability data deemed necessary.
EES	Withhold	16 Sep 2010	Withhold
Pharm/Tox	Approvable	11-December-2009	Refer to final P/T review by M. Brower.
Biopharm	Acceptable	12-February-2009	Refer to review by Jeanne Fourie.
LNC	N/A		
Methods Validation	N/A		Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Categorical exclusion (see review)		See Review #1.
Microbiology	Approvable pending revision – deficiencies noted	08-JAN-2010 and 01-SEP-2010	Refer to review by S. Langille. Await review for the comparability protocol submitted in Amendment dated 24-NOV-2009
DMEPA	Additional areas for improvements are identified.	26-JAN-2010	Refer to the 26-JAN-2010 Label and Labeling Review by Loretta Holmes. Applicant has addressed the issues cited in the C/R dated 28-APR-2009. Additional areas are identified in submission dated 29-JUL-2009.

The CMC Review for NDA 22-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective until acceptable container/carton and PI labeling are submitted. Also note that a withhold overall recommendation dated 16-SEP-2010 was issued by the Office of Compliance. GMP status of the manufacturing and controls facilities are as follows:

1. Apotex, Signet Campus, Toronto, Canada – Withhold and Warning Letter issued on 29-MAR-2010
2. Apotex, 3701 Weston Road, Toronto, Canada – Withhold and Warning Letter issued on 29-MAR-2010
3. Apotex, 380 Elgin Mills Road, Richmond Hill, Ontario, Canada – Withhold on 25-MAY-2010 based on DO recommendation.
4. Apotex, 50 Steinway, Etobicoke, Ontario, Canada – Withhold and Warning Letter issued on 25-JUN-2009

(b) (4)

Include the following deficiencies in the action letter:

1. The proposed established name "Docetaxel Injection (b) (4) is not acceptable in that (b) (4) is not a recognized name by the United States Pharmacopeia. We recommend that you revise your established name to "Docetaxel Injection" in the package insert, container labels and carton labels.

2. Revise your labels as follows:

Container Labels

A. Active Drug
   a. On the 80 mg/2 mL vial, the statement of strength and "Before Initial Dilution" statement are (b) (4) difficult to read. Revise accordingly (e.g., increase the font weight) to improve readability.

b. Add the statement "For Intravenous Infusion Only After Final Dilution" and place it below the statement "Before Initial Dilution" on the principal display panel. Consider deleting (b) (4) to provide additional space, if needed.
c. Increase the prominence of the statement of strength on the 20 mg/0.5 mL and 80 mg/2 mL vials.

B. Diluent

a. Decrease the prominence of the Docetaxel Injection (b) (4) strength (i.e., "20 mg" and "80 mg") to be commensurate with the statement "for Docetaxel Injection (b) (4)

b. The diluent ingredients are not stated on the label. State the diluent ingredients.

Carton Labels:

A. Increase the prominence of the statement of strength on the 20 mg/0.5 mL and 80 mg/2 mL vials.

B. On the side panel, expand the box around the caution statement to include the "10 mg/mL docetaxel after initial dilution...to prepare the final dilution for infusion" statement.

3. The proposed sites for the manufacturing and control of the drug product do not meet current GMP requirements. Specifically, the Apotex facility at Richmond Hill has unresolved GMP issues from a recent inspection; and the sites at Weston Road, Signet Campus, and Etobicoke have unresolved GMP issues addressed in Warning Letters dated 25-JUN-2009 and 29-MAR-2010. Satisfactory resolution of these deficiencies is required before this application may be approved.

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

None

II. Summary of CMC Assessments (See CMC review #1)

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

(1) Drug Substance

Docetaxel anhydrous is a white to off white crystalline powder. (b) (4) The anhydrous form of docetaxel is being used in this product. This form is practically insoluble in water, it is slightly soluble in chloroform and highly soluble in methanol, ethanol and acetone.

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 [redacted] (b) (4) that is routinely monitored in the drug product.

Manufacturing information is provided in the DMF [redacted] (b) (4)

For testing of the drug substance, apart from the tests reported in the Certificate Of Analysis (COA) by the manufacturer [redacted] (b) (4), the sponsor has developed an in-house GC based method to confirm presence of residual solvents and an in-house HPLC based method to confirm detection in-organic impurities and assay. All acceptance criteria set were in accordance with ICH guidances. Batch data for two lots of drug substance that were used to manufacture the pilot stability drug product lots is provided in the NDA.

Docetaxel anhydrous is hygroscopic in high humidity. It is thus packed in [redacted] (b) (4) It is to be stored protected from light in the suggested packaging configuration at 20 to 25ºC, and a retest period of [redacted] (b) (4) is proposed. The DMF was found adequate (See J.Jee Review dated 30-NOV-2009).

(2) Drug Product

The drug product is available as 40 mg/mL concentrate solution of Docetaxel Anhydrous (API) in Polyethylene Glycol 300 NF (PEG-300) for Injection. This NDA is filed as a 505b(2) submission. The drug product is pharmaceutically equivalent to the Reference Listed Drug (RLD), Taxotere for injection (NDA 20-449) marketed by Sanofi Aventis. For this NDA, the sponsor developed docetaxel injection at the same therapeutic concentration as Taxotere in the infusion solution but with a different qualitative and quantitative formulation as compared to the RLD for both the injection concentrate as well as the diluent. The sponsor has not proposed any trade name for this product and does not intend to do so.

For this application, the sponsor requested a biowaiver in accordance with 21 CFR 320.22(b)(1). Their rationale is that since this is an intravenously administered product, the difference in excipient composition between the final dilution for injection between this product and the RLD would be self evident, and is not expected to have any impact on the safety and efficacy of the drug. This reviewer is in concurrence with this opinion since the starting dose is the same for both Apotex's product and the RLD. Furthermore, at the pre NDA meeting on September 26, 2007 for IND 78,376, the agency had communicated to the sponsor that a clinical study in support of this application is not required.

In the same fashion as the RLD, docetaxel injection is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of Docetaxel Anhydrous. In this case, the sponsor chose Polyethylene Glycol (PEG) 300 in place of Polysorbate 80, as in the RLD for the injection concentrate. The injection concentrate also requires dilution prior to use. It is diluted by adding to it the entire withdrawable content of the accompanying diluent vial. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. This initial diluted solution (at a concentration of Docetaxel Anhydrous 10 mg/mL) is further diluted with an appropriate volume of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to produce a final dilution for IV infusion at a concentration of 0.3 mg/mL to 0.74 mg/mL Docetaxel. All utilized excipients are compendial grade.

CMC Assessment Section

The choice of manufacturing process for both the injection concentrate as well as the diluent was made on the basis of prior experience. The injection concentrate is manufactured at a (b) (4) The sponsor provided scale-up information of the injection concentrate (b) (4) as a major amendment dated March 29, 2009 and was reviewed in this cycle; microbiology recommended approval. Bulks for both the concentrate as well as the diluent are to be stored between 20-25ºC, protected from light. Amendment 29-JUL-2009 was a complete response to the FDA Action Letter dated 28-APR-2009, and amendment dated 24-NOV-2009 was submitted to propose (b) (4) for the Docetaxel Diluent, specifically, (b) (4) at the Richmond Hill facility. The information provided in the 24-NOV-2009 amendment does not have any CMC issues and the Microbiology Review dated 17-SEP-2010 recommended approval. However, the Richmond Hill facility is deemed unacceptable by the Office of Compliance.

The injection concentrate specifications include quality tests for appearance, identity, assay, degradation products, and microbiology. In the original submission, it was noted that the specifications for release were (b) (4) the sponsor proposed the same set of specifications for both release and stability. It is noted from the specifications that four of the impurities are above the ICH Q3B(R2) limit of 0.2% and would thus have to be qualified. These are: (b) (4) In addition, it is not clear from the March 12, 2009 amendment whether the impurity (b) (4) is at all present in the product and if so at what levels. Pharmacology/Toxicology review concluded that the proposed limits are acceptable for safety. Please refer to the Pharmacology/Toxicology review for further details regarding impurity qualification (refer review by M. Brower dated 21-April, 2009).

Docetaxel Injection (b) (4), 20 mg/0.5 mL is packaged in 5 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover, while 80 mg/2 mL is packaged in 10 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover.

The diluent that is supplied with the injection concentrate contains polysorbate 80, NF and alcohol (b) (4) USP (Ethyl Alcohol) in Water for Injection, USP/EP.. Polysorbate 80 is used as a (b) (4) The RLD's diluent on the other hand is composed entirely of ethyl alcohol.

The current NDA submission also included a proposed (b) (4) protocol submitted on 29-JUL-2009. This protocol allowed for the (b) (4) This protocol was reviewed by Microbiology (see Reviews dated 08-JAN-2010 and 01-SEP-2010) and recommended that it was not acceptable. Apotex withdrew this (b) (4) protocol on 31-AUG-2010. (b) (4), the comparability protocol submitted on 24-NOV-2009 Amendment was reviewed by Microbiology on 17-SEP-2010 and recommended approval.

Amendment dated 24-MAR-2010 provided response to Complete Response Letter dated 29-JAN-2010, CMC Microbiology recommended approval on 17-SEP-2010.

On evaluation of the stability data, it was decided to grant the sponsor only 18 months of expiration, if the application were to be approved at this time. (b) (4) In addition, granting the 18 month expiration per the 18 month data provided is in accordance with ICH guidance Q1E, which states that no extrapolation be allowed if significant changes are observed during storage. This was conveyed on the 29-JAN-2010 Complete Response Letter.

The submitted labels and labeling have been reviewed for this submission by Division of Medicine Error Prevention and Analysis (DMEPA). Several deficiencies, identified in their 27-FEB-2009 Review, were sent in the 28-APR-2009 Complete Response Letter. Apotex submitted their revisions on 29-JUL-2009. The revised carton and container labels were reviewed on 26-JAN-2010 by the DMEPA and this review concluded that the applicant have addressed all their comments; however, DMEPA have identified additional areas that need improvement and should be changed prior to approval; see comments sent to applicant, Executive Summary, I A Recommendation and Conclusion on Approvability.

The overall recommendation dated 16-SEP-2010 from the Office of Compliance is "Withhold". In addition, issues addressed in Warning Letters were on 25-JUN-2009 and 29-MAR-2010 for Apotex facilities at Signet Campus, Toronto, Canada; 3701 Weston Road, Toronto, Canada; 50 Steinway Blvd., and Etobicoke, Ontario, Canada are unresolved; see attachment A.

B. Recommendation and Conclusion on Approvability

This application is not recommended for approval, see comment under II D

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

Docetaxel Injection is a microtubule inhibitor used for:
Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

This drug is administered intravenously over 1 hour every 3 weeks in patients pre-medicated with oral corticosteroids.

D. Basis for Approvability or Not-Approval Recommendation

The application cannot be recommended for approval under section 505 of the Act from a chemistry, manufacturing and controls perspective until acceptable container/carton and PI labeling are submitted. Also note that a withhold overall recommendation dated 16-SEP-2010 was issued by the Office of Compliance. Satisfactory resolution of these deficiencies is required before this application may be approved.

III. Administrative

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary. It includes two drug product sections: one for the concentrate and another for the diluent.

C. CC Block: entered electronically in DARRTS

30 Page(s) have 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/

JOSEPHINE M JEE
09/22/2010

WILLIAM M ADAMS
09/22/2010
William Adams, acting for Sarah Pope Miksinski

NDA 22-312

Docetaxel Injection

Apotex, Inc.

Josephine Jee

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 22-312

2. REVIEW #: 2

3. REVIEW DATE: 09-DEC-2009

4. REVIEWER: Josephine Jee

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original Submission	03-Mar-2008
Correspondence (C)	27-MAR-2009
Amendment # 3 (BC)	17-Sept-2008
Amendment #4 (AC)	3-Dec-2008
Amendment # 5 (BC)	5-March-009
Amendment # 7 (BC)	12-March-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (BC) Response to 12-JAN-2009 Letter	31-MAR-2009
Amendment (BL)	29-JUL-2009
Amendment (QR) – Response to 28-APR-2009 Letter	29-JUL-2009
Amendment (NR)	14-AUG-2009
Amendment (QR) Tel. Request.	10-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex, Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada, M9L1T9
Representative:	Kiran Krishnan
Telephone:	954-384-3986

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Docetaxel Injection
c) Code Name/# (ONDC only): NA

d) Chem. Type/Submission Priority (ONDC only):

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

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 40 mg/mL (20 mg/0.5mL and 80mg/2mL)

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: ✔ Rx ___OTC

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

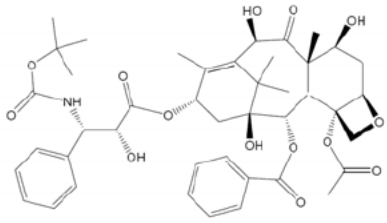
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Chemical Name: 2aR-(2aα, 4β, 4aβ, 6β, 9α, (αR*, βS*), 11α, 12α, 12aα,12bα)]- β-[[(1, 1-dimethylethoxy)carbonyl]amino]- α-hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)- 2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12bdodecahydro-4, 6, 11-trehydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl]ester

Molecular Structure:



Molecular Formula: $C_{43}H_{53}NO_{14}$ Molecular Weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel anhydrous drug substance	1	Adequate	30-NOV-2009	See DMF review by J.Jee
	III		(b) (4)	1	Adequate	22-SEP-2003	By David Lewis
	V			1	Adequate	04-APR-2008	By John Arigo
	III			1	Adequate	22-APR-2009	By Sharmista Chatterjee
	V			1	Adequate	12-JUN-2009	By J. Wells

[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)

B. Other Documents:

NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ COMMENTS
Biometrics	N/A		No statistical analysis of drug product stability data deemed necessary.
EES	Withhold	08-JAN-2010	Withhold
Pharm/Tox	Approvable	11-December-2009	Refer to final P/T review by M. Brower.
Biopharm	Acceptable	12-February-2009	Refer to review by Jeanne Fourie.
LNC	N/A		
Methods Validation	N/A		Conventional methods not meeting the ONDQA criteria for requesting method validation.
EA	Categorical exclusion (see review)		See Review #1.
Microbiology	Approvable pending revision – deficiencies noted	08-JAN-2010	Refer to review by S. Langille.
DMEPA	Outstanding comments from last review cycle; updated consult review still pending		Refer to the previous review by Loretta Holmes. Also refer to the discussion in the Labeling section of this review and updated consult review (not yet filed).

The CMC Review for NDA 22-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval from a chemistry, manufacturing and controls under section 505 of the Act, until acceptable container/carton and PI labeling are submitted, an acceptable microbiology recommendation is received, and the following outstanding deficiencies are adequately addressed. Also note that a withhold overall recommendation dated 08-JAN-2010 was received from the Office of Compliance

Include the following deficiencies in the action letter:

1. Given the breadth of information provided in the November 24, 2009 amendment, as well as the timing of this submission, this amendment (which includes the use of (b) (4) at the Richmond Hill facility (b) (4) of Docetaxel Diluent, 1.8 mL and 7.1 mL package sizes) was not reviewed during this cycle.

2. Your (b) (4) protocol submitted on the 29-JUL-2009 Amendment (b) (4) is inadequate based on the Microbiology evaluation. Refer to Microbiology deficiencies.

3. Note the following outstanding deficiencies regarding your proposed carton labels:
   a) The preparation instructions for the dilution for infusion are absent.
   b) Increase the prominence of the statement "Caution: Cytotoxic agent."
   c) The prominence of the Warning "Keep out of reach of children" should be Increased.
   e) Add the word "Sterile".
   f) Include an "Each mL contains…" statement.
   g) Identify the location for lot no. and expiration date.
   h) The NDC numbers do not match with the container labels. Clarify this discrepancy.

4. Note the following outstanding deficiencies regarding your proposed container labels:
   a) Provide the storage condition statement.
   b) Provide the statement "Protect from light."
   c) Include a space for lot no. and expiration date
   d) Add the word "Sterile" and Single Use Vial."

e) Include the statement "Caution: Cytotoxic Agent."
f) Add the statement "Warning: Keep out of reach of children."
g) The NDC numbers do not match with the carton labels. Clarify this discrepancy.

5. Note the following outstanding deficiencies regarding your proposed Package Insert:
   a) In Item 11 – Description, state the chemical name as: (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β,- 2α- epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2- benzoate.
   b) Section 16.1 does not list the NDC numbers for the Diluents.
   c) The NDC numbers listed in Section 16.1 match with the carton labels but not with the container labels. Clarify this discrepancy.
   d) In Section 16.1, list all NDC numbers assigned to carton and container labels.

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

None

II. Summary of CMC Assessments (See CMC review #1)

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

(1) Drug Substance

Docetaxel anhydrous is a white to off white crystalline powder. (b) (4) The anhydrous form of docetaxel is being used in this product. This form is practically insoluble in water, it is slightly soluble in chloroform and highly soluble in methanol, ethanol and acetone.

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 (b) (4) that is routinely monitored in the drug product.

Manufacturing information is provided in the DMF (b) (4)

For testing of the drug substance, apart from the tests reported in the Certificate Of Analysis (COA) by the manufacturer (b) (4), the sponsor also developed an in-house GC based method to confirm presence of residual solvents and an in-house HPLC based method to confirm detection in-organic impurities and assay. All acceptance criteria set were in accordance with ICH guidance's. Batch data for two lots of drug

substance that were used to manufacture the pilot stability drug product lots is provided in the NDA.

Docetaxel anhydrous is hygroscopic in high humidity. It is thus packed in (b) (4) It is to be stored protected from light in the suggested packaging configuration at 20 to 25ºC, and a retest period of (b) (4) is proposed. The DMF was found adequate (See J.Jee Review dated 30-NOV-2009).

(2) Drug Product

The drug product is available as 40 mg/mL concentrate solution of Docetaxel Anhydrous (API) in Polyethylene Glycol 300 NF (PEG-300) for Injection. This NDA is filed as a 505b(2). The drug product is pharmaceutically equivalent to the Reference Listed Drug (RLD), Taxotere for injection (NDA 20-449) marketed by Sanofi Aventis. For this NDA, the sponsor developed docetaxel injection at the same therapeutic concentration as Taxotere in the infusion solution but with a different qualitative and quantitative formulation as compared to the RLD for both the injection concentrate as well as the diluent. The sponsor has not proposed any trade name for this product and does not intend to do so.

For this application, the sponsor requested a biowaiver in accordance with 21 CFR 320.22(b)(1). Their rationale is that since this is an intravenously administered product, the difference in excipient composition between the final dilution for injection between this product and the RLD would be self evident, and is not expected to have any impact on the safety and efficacy of the drug. This reviewer is in concurrence with this opinion since the starting dose is the same for both Apotex's product and the RLD. Furthermore, at the pre NDA meeting on September 26, 2007 for IND 78,376, the agency had communicated to the sponsor that a clinical study in support of this application is not required.

In the same fashion as the RLD, docetaxel injection is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of Docetaxel Anhydrous. In this case, the sponsor chose Polyethylene Glycol (PEG) 300 in place of polysorbate 80, as in the RLD for the injection concentrate. The injection concentrate also requires dilution prior to use. It is diluted by adding to it the entire withdrawable content of the accompanying diluent vial. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. This initial diluted solution (at a concentration of Docetaxel Anhydrous 10 mg/mL) is further diluted with an appropriate volume of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to produce a final dilution for IV infusion at a concentration of Docetaxel Anhydrous 0.3 mg/mL to 0.74 mg/mL. All utilized excipients are compendial.

The choice of manufacturing process for both the injection concentrate as well as the diluent was done on the basis of prior experience. The injection concentrate is manufactured at a [redacted]. The sponsor provided scale up information of the injection concentrate to [redacted] as a major amendment dated March 29, 2009 and was reviewed in this cycle pending microbiology recommendation. Bulks for both the concentrate as well as the diluent are to be stored between 20-25ºC, protected from light. Amendment 29-JUL-2009 was a complete response to the FDA Action Letter dated 28-APR-2009, and amendment dated 24-NOV-2009 was submitted to propose [redacted] for the Docetaxel Diluent, specifically [redacted] at the Richmond Hill facility. Given the breath of the information provided in the 24-NOV-2009 amendment, as well as the timing of the submission, this amendment was not reviewed during this cycle.

The injection concentrate specifications include quality tests for appearance, identity, assay, degradation products, and microbiology. In the original submission, it was noted that the specifications for release were [redacted] the sponsor proposed the same set of specifications for both release and stability. It is noted from the specifications that four of the impurities are above the ICH Q3B(R2) limit of 0.2% and would thus have to be qualified. These are: [redacted] In addition, it is not clear from the March 12, 2009 amendment whether the impurity [redacted] is at all present in the product and if so at what levels. Please refer to the Pharmacology/Toxicology review for further details regarding impurity qualification (refer review by M. Brower dated 21-April, 2009).

Docetaxel Injection [redacted], 20 mg/0.5 mL is packaged in 5 mL clear glass vials (13 mm) with grey [redacted] serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a [redacted] cover, while 80 mg/2 mL is packaged in 10 mL clear glass vials (13 mm) with grey [redacted] serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a [redacted] cover.

The diluent that is supplied with the injection concentrate contains polysorbate 80 NF and alcohol [redacted] USP (Ethyl Alcohol) in Water for Injection USP/EP.. Polysorbate 80 is used as a [redacted] The RLD's diluent on the other hand is composed entirely of ethyl alcohol.

The current NDA submission also included a proposed [redacted] protocol. This protocol allowed for th [redacted]

(b) (4) Due to the pending Microbiology deficiencies (S. Langille Review dated 08-JAN-2010), it is not possible to confirm the acceptability of the proposed (b) (4) protocol at this time. This will be communicated in the action letter.

On evaluation of the stability data, it was decided to grant the sponsor only 18 months of expiration, if the application were to be approved at this time. (b) (4) In addition, granting the 18 month expiration per the 18 month data provided is in accordance with ICH guidance Q1E, which states that no extrapolation be allowed if significant changes are observed during storage.

Complete review of labeling has been reviewed at this time for this submission and several deficiencies have been identified. Comments based on the proposed container/carton label and labeling will be communicated to the applicant. A consult review was requested from DMEPA on 08-OCT-2009 and has not yet been received as of the date of this review.

Given the breath of information and the timing of amendments dated 24-NOV-2009, which provides (b) (4) for the Docetaxel Diluent, and 14-JAN-2010, which provides for the withdrawal of an alternate analytical testing site, (b) (4) they were not reviewed during this cycle.

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

Docetaxel Injection is a microtubule inhibitor used for:
Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

This drug is administered intravenously over 1 hour every 3 weeks in patients pre-medicated with oral corticosteroids.

C. Basis for Approvability or Not-Approval Recommendation

The application cannot be recommended for approval from a chemistry, manufacturing and controls until acceptable container/carton and PI labeling are submitted, an acceptable microbiology recommendation is received, and several outstanding CMC deficiencies are adequately addressed. Also note that a withhold overall recommendation dated 08-JAN-2010 was received from the Office of Compliance

III. Administrative

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary. It includes two drug product sections: one for the concentrate and another for the diluent.

C. CC Block: entered electronically in DFS

44 Page(s) have been Withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22312	ORIG-1		DOCETAXEL INJECTION 40 MG ML

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
01/22/2010

Sarah Pope Miksinski
01/22/2010

HARIPADA SARKER
01/22/2010

42 Page(s) have been Withheld in full as b4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name / Subject
MF (b) (4)	(b) (4)	DOCETAXEL ANHYDROUS, NON-STERILE BULK DRUG SUBSTANCE AS MANUFACTURED BY (b) (4)

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

/s/

SHARMISTA CHATTERJEE
04/22/2009

SARAH C POPE
04/22/2009

NDA 22-312

Docetaxel Injection

Apotex,Inc.

Sharmista Chatterjee, Ph.D.

Office of New Drug Quality Assessment

For the Division of Drug Oncology Products

Table of Contents

CMC Review Data Sheet

1. NDA 22-312

2. REVIEW #: 1

3. REVIEW DATE: 23- April-2009

4. REVIEWER: Sharmista Chatterjee, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	03-Mar-2008
Correspondence (C)	
Amendment # 3 (BC)	17-Sept-2008
Amendment #4 (AC)	3-Dec-2008
Amendment # 5 (BC)	5-March-2009
Amendment # 7 (BC)	12-March-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex, Inc.
Address:	150 Signet Drive, Toronto, Ontario, Canada, M9L1T9
Representative:	Kiran Krishnan
Telephone:	954-384-3986

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

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

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Injectable

12. STRENGTH/POTENCY: 40 mg/mL (20 mg/0.5mL and 80mg/2mL)

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: ✔ Rx ___OTC

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

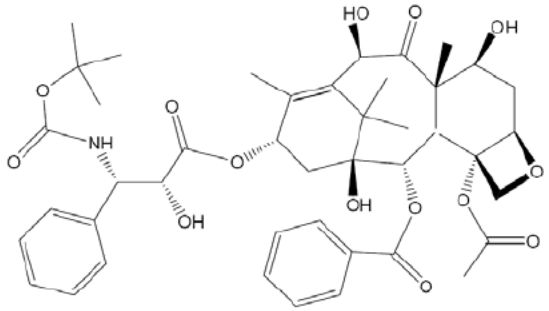
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

Chemical Name: 2aR-(2aα, 4β, 4aβ, 6β, 9α, (αR*, βS*), 11α, 12α, 12aα, 12bα)]- β-[[(1, 1-dimethylethoxy)carbonyl]amino]- α-hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)- 2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12bdodecahydro-4, 6, 11-trehydroxy-4a, 8, 13, 13-tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl]ester

Molecular Structure:



Molecular Formula: $C_{43}H_{53}NO_{14}$

Molecular Weight: 807.88

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Docetaxel anhydrous drug substance	1	Inadequate	April-22-2009	See DMF review by Sharmista Chatterjee
	III		(b) (4)	1	Adequate	Sept-22-2003	By David Lewis
	V			1	Adequate	April-4-2008	By John Arigo
	III			1	Adequate	April-22-2009	By Sharmista Chatterjee

[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)

B. Other Documents:

NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER/ COMMENTS
Biometrics	N/A		No statistical analysis of drug product stability data deemed necessary.
EES	Pending		Pending as of April 23, 2009
Pharm/Tox	Approvable	21-April-2009	Refer to final P/T review by M. Brower.
Biopharm	Acceptable	12-February-2009	Refer to review by Jeanne Fourie.
LNC	N/A		
Methods Validation	N/A		Conventional methods not meeting the ONDQA criteria for requesting method validation.
OPDRA			
EA	Categorical exclusion (see review)		
Microbiology	Recommended Approval	20-March-2009	Refer to review by Stephen Langille
DMEPA	Current label not acceptable	27-February-2009	Refer to the review by Loretta Holmes Also refer discussion in the Labeling section of this review.

The CMC Review for NDA 22-312

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval from a chemistry, manufacturing and controls under section 505 of the Act, until acceptable container/carton and PI labeling are submitted and the following outstanding deficiencies are adequately addressed. Include the following comments in the action letter:

1. Demonstrate that [redacted] (b) (4) levels in the drug product both during release as well as during stability are below the ICH Q3B proposed limit of 0.2%.

2. Demonstrate the adequacy of the proposed analytical (Method No. DOCE-SINJ-CB-90-RH) method in terms of precision, linearity, accuracy and robustness for all the degradants monitored in the docetaxel injection concentrate that are over 0.2%.

3. Considering that all vials are for single use, revise the 'Volume of Injection' acceptance criteria for docetaxel injection diluent to represent the actual fill volumes, as listed in table 3 of the package insert (for 1.8mL the range is 1.83-2.43mL while for 7.1mL the range is 7.3-7.9mL).

4. Describe your plans to scale up in order to meet the commercial requirement.

Additionally, include the following comments in the action letter:

1. Given the breadth of information provided in the March 31, 2009 amendment, as well as the timing of the submission, this amendment (includes scale up information) was not reviewed during this cycle.

2. Due to the outstanding Chemistry, Manufacturing and Controls deficiencies, it is not possible to confirm the acceptability of your proposed [redacted] (b) (4) Protocol.

   Note that an overall acceptable determination from the Office of Compliance has not yet been received, as of 23-APR_2009.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Docetaxel anhydrous is a white to off white crystalline powder. (b) (4) The anhydrous form of docetaxel is being used in this product. This form is practically insoluble in water, it is slightly soluble in chloroform and highly soluble in methanol, ethanol and acetone.

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 (b) (4) that is routinely monitored in the drug product.

Manufacturing information is provided in the DMF (b) (4)

For testing of the drug substance, apart from the tests reported in the Certificate Of Analysis (COA) by the manufacturer (b) (4), the sponsor also developed an in-house GC based method to confirm presence of residual solvents and an in-house HPLC based method to confirm detection in-organic impurities and assay. All acceptance criteria set were in accordance with ICH guidance's. Batch data for two lots of drug substance that were used to manufacture the pilot stability drug product lots is provided in the NDA.

Docetaxel anhydrous is hygroscopic in high humidity. It is thus packed in (b) (4) It is to be stored protected from light in the suggested packaging configuration at 20 to 25°C, and a shelf life (b) (4) is proposed. The DMF was found to be inadequate (refer review by S.Chatterjee).

(2) Drug Product

The drug product is available as 40 mg/mL concentrate solution of Docetaxel Anhydrous (API) in Polyethylene Glycol 300 NF (PEG-300) for Injection. This NDA is filed as a 505b(2). The drug product is pharmaceutically equivalent to the Reference Listed Drug (RLD), Taxotere for injection (NDA 20-449) marketed by Sanofi Aventis. For this NDA,

the sponsor developed docetaxel injection at the same therapeutic concentration as Taxotere in the infusion solution but with a different qualitative and quantitative formulation as compared to the RLD for both the injection concentrate as well as the diluent. The sponsor has not proposed any trade name for this product and does not intend to do so.

For this application, the sponsor requested a biowaiver in accordance with 21 CFR 320.22(b)(1). Their rationale is that since this is an intravenously administered product, the difference in excipient composition between the final dilution for injection between this product and the RLD would be self evident, and is not expected to have any impact on the safety and efficacy of the drug. This reviewer is in concurrence with this opinion since the starting dose is the same for both Apotex's product and the RLD. Furthermore, at the pre NDA meeting on September 26, 2007 for IND 78,376, the agency had communicated to the sponsor that a clinical study in support of this application is not required.

In the same fashion as the RLD, docetaxel injection is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of Docetaxel Anhydrous. In this case, the sponsor chose Polyethylene Glycol (PEG) 300 in place of polysorbate 80, as in the RLD for the injection concentrate. The injection concentrate also requires dilution prior to use. It is diluted by adding to it the entire withdrawable content of the accompanying diluent vial. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. This initial diluted solution (at a concentration of Docetaxel Anhydrous 10 mg/mL) is further diluted with an appropriate volume of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to produce a final dilution for IV infusion at a concentration of Docetaxel Anhydrous 0.3 mg/mL to 0.74 mg/mL. All utilized excipients are compendial.

The choice of manufacturing process for both the injection concentrate as well as the diluent was done on the basis of prior experience. The injection concentrate is manufactured at a (b) (4) The sponsor provided scale up information of the injection concentrate to (b) (4) as a major amendment dated March 29, 2009. Given the size of the amendment and proximity of the submission date to the PDUFA date, it was not reviewed during this cycle. Bulks for both the concentrate as well as the diluent are to be stored between 20-25ºC, protected from light.

The injection concentrate specifications include quality tests for appearance, identity, assay, degradation products, and microbiology. In the original submission, it was noted that the specifications for release were (b) (4) the sponsor proposed the same set of specifications for both release and stability. It is noted from the specifications that four of

the impurities are above the ICH Q3B(R2) limit of 0.2% and would thus have to be qualified. These are: (b) (4) In addition, it is not clear from the March 12, 2009 amendment whether the impurity (b) (4) is at all present in the product and if so at what levels. Please refer to the Pharmacology/Toxicology review for further details regarding impurity qualification (refer review by M. Brower dated 21-April, 2009).

Docetaxel Injection (b) (4) 20 mg/0.5 mL is packaged in 5 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) e cover, while 80 mg/2 mL is packaged in 10 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover.

The diluent that is supplied with the injection concentrate contains polysorbate 80 NF and alcohol (b) (4) USP (Ethyl Alcohol) in Water for Injection USP/EP.. Polysorbate 80 is used as a (b) (4) The RLD's diluent on the other hand is composed entirely of ethyl alcohol.

The current NDA submission also included a proposed (b) (4) protocol. This protocol allowed for the (b) (4) Due to the pending CMC deficiencies, it is not possible to confirm the acceptability of the proposed (b) (4) protocol at this time. This will be communicated in the action letter.

On evaluation of the stability data, it was decided to grant the sponsor only 12 months of expiration, if the application were to be approved at this time. (b) (4) In addition, granting the 12 month expiration per the 12 month data provided is in accordance with ICH guidance Q1E, which states that no extrapolation be allowed if significant changes are observed during storage.

Complete review of labeling has been deferred at this time for this submission given the outstanding CMC deficiencies. Comments based on the proposed container/carton label were communicated to DMEPA. For further discussion about container/carton labeling refer to the review by L.Holmes in DFS dated February 27,2009.

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

Docetaxel Injection is a microtubule inhibitor used for:

Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer

Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction

Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN

This drug is administered intravenously over 1 hour every 3 weeks in patients pre-medicated with oral corticosteroids.

C. Basis for Approvability or Not-Approval Recommendation

Satisfactory resolution of all the CMC deficiencies outlined in section A, as well as a review of the proposed (b) (4) protocol provided in the original NDA and scale up information provided in the amendment dated March 31, 2009, is required before an approval recommendation can be made from the CMC stand point. Additionally, an acceptable recommendation is needed from the Office of Compliance prior to a recommendation for CMC approval.

III. Administrative

This NDA was submitted electronically as a 505b(2) application. It is in eCTD format and includes a Quality Overall Summary. It includes two drug product sections: one for the concentrate and another for the diluent.

C. CC Block: entered electronically in DFS

102 Page(s) have 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/

Sharmista Chatterjee
4/23/2009 04:04:49 PM
CHEMIST

Sarah Pope
4/23/2009 04:29:04 PM
CHEMIST

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

OND Division:	Division of Drug Oncology Products
NDA:	22-312
Applicant:	Apotex, Inc.
Letter Date:	27 March, 2008
Stamp Date:	28 March, 2008
PDUFA Goal Date:	28 January, 2009 (standard)
Tradename:	Docetaxel Injection
Established Name:	Docetaxel
Dosage Form/Strength:	Injection - 40 mg/mL (0.5mL and 2mL)
Route of Administration:	IV
Indication:	Patients with locally advanced or metastatic breast cancer following failure of prior chemotherapy.

Regulatory Filing	For 505 (b) (2)
Related IND	IND 78,376
Assessed by:	Haripada Sarker

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

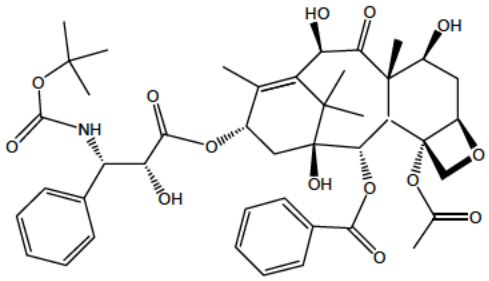
Background Summary
The application introduces the drug product, Docetaxel Injection, which is supplied as 40mg/ml solution of two strengths. Docetaxel Injection is diluted with appropriate volumes of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to form the final dilution for infusion at a concentration of Docetaxel Anhydrous 0.3 mg to 0.74 mg/mL. The following detail indication for DP provided: Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC; Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC; Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer; Gastric Adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction; Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

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. It is noted that Taxotere® under NDA 20-449 is considered as the reference listed drug (RLD), where the formulation is equivalent (40mg base/mL), except that a different excipient is used in the Apotex DP.

No pre-NDA meeting with CMC issue is indicated as per DARRTS document search. However, applicant has made communications to the Agency for clinical pharmacology issues. The CMC information of the NDA is submitted as per CTDQ format.

Drug Substance (DS)

Applicant referred to DMF (b) (4) by (b) (4) for DS CMC information. In the NDA submission, applicant provided brief DS information regarding identity, physico-chemical properties and specifications. Docetaxel is an optically active compound. It is a (b) (4) drug substance made from (b) (4) 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 (b) (4) 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 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.
- EER information for DS needs to be re-examined for accuracy.
- (b) (4) is the new DS manufacturer of Docetaxel (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.
- The role of additional DMF (b) (4) that is noted under listing of the manufacturing and control sites.

Drug Product (DP)

The finished drug product is a solution. Docetaxel Anhydrous (API) in Glycol 300 NF (PEG-300) solution at 40 mg/mL in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL is termed as injection concentrates. The injection concentrate requires dilution prior to use. The diluents contain Polysorbate 80 NF and Alcohol (b) (4) USP (Ethyl Alcohol) in Water for Injection USP/EP. This initial diluted solution (10 mg/mL) needs to be further diluted with an appropriate volume of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to produce a final dilution for IV infusion at a concentration of Docetaxel Anhydrous 0.3 mg/mL to 0.74 mg/mL. Since the DP requires dilution prior to administration, there are two DP sections provided separately in the body of the data: one for concentrate and the other for the diluent.

A comparative composition between the RLD and the DP of this submission is provided. Applicant utilizes the DP pharmaceutical development experiences of RLD to develop Docetaxel injection for this submission. (b) (4)

The proposed manufacturing site is listed below:

Apotex Inc. – Richmond Hill Site
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Docetaxel Injection (b) (4) 40 mg/mL (20 mg/0.5 mL) will be packaged in 5 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover.

Docetaxel Injection (b) (4), 40 mg/mL (80 mg/2 mL) will be packaged in 10 mL clear glass vials (13 mm) with grey (b) (4) serum stoppers (13 mm) and aluminum crimp caps (13 mm) with a (b) (4) cover.

Two different acceptance criteria for DP impurities are proposed for release and for stability specification as following.

Degradation Products	DP Release Limits	DP Stability Limits
(b) (4)		

Stability profiles for both Docetaxel concentrate and infusion solution are provided for long term and accelerated conditions as following.

Storage Description	Storage Conditions/ Orientation	Completed (and Proposed) Test Intervals
Shelf-Life (concentrate)	25°C (±2°C) / 60% (±5%) RH - Inverted	0, 3, (6, 9, 12, 18 and 24) months
	25°C (±2°C) / 60% (±5%) RH – Vertical	0, 3, (6, 9, 12, 18 and 24) months
Accelerated (concentrate)	40°C (±2°C) /75% (±5%) RH - Inverted	0, 1, 2, 3 (and 6*) months
	40°C (±2°C) /75% (±5%) RH - Vertical	0, 1, 2, 3 (and 6*) months
Cycling (concentrate)**	-10°C to -20°C / 40°C (±2°C) / 75% (±5%) RH - Vertical	0 and 3 cycles
Light (concentrate) (covered and uncovered)	NLT 1.2 million lux hours and NLT 200 watt hours/m^2 - Horizontal	0 and 7 days
Room Temperature (Constituted Solution)	15°C to 30°C - Vertical	0 and 8 Hours
Refrigerated (Constituted Solution)	2°C to 8°C - Vertical	0 and 8 Hours

* Optional
** Three cycles, each with NLT 2 days at -10 C to -20 C and then NLT 2 days at 40 C (±2 C) / 75% (±5%) RH

No statistical analysis is included to support the proposed DP expiration dating. Applicant indicated to update the stability data as available. The Applicant proposes a 24-month expiration dating period for the Docetaxel concentrate, when stored 25°C (±2°C) / 60% (±5%) RH in absence of light.

Drug Product Critical Issues

- (b) (4) 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.
- Two different acceptance criteria for DP impurities are proposed for release and for stability specification. Enough justification should be provided to qualify the level.
- Justification of 24-months expiration based on 3-months stability data and whether ICH Q1E can be applied for this extrapolation.
- The DP labeling, which is submitted in PRL format, need to be evaluated for its relevant CMC sections.

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?	√		
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?	√		**No**.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Not applicable. No CMC issue in pre-NDA meeting.
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/CBER LNC DMETS/ODS EER

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

DMF Number	Holder	Description	LOA Included
[redacted] (b) (4)			Yes
			Yes
			Yes
			Yes

Additional DMF [redacted] (b) (4) is noted under listing of the manufacturing and control sites. Rest of the DMF numbers is listed in FDA Form 1571.

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)	May 20, 2008 Date
Ravi Harapanhalli, Ph.D. Branch Chief	March 20, 2008 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
5/21/2008 11:12:25 AM
CHEMIST

Ravi Harapanhalli
5/21/2008 11:44:40 AM
CHEMIST
Correct IQA is being placed. The earlier wrong IQA will be deleted from the DFS.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

A on:	NDA 22312/000	**Action Goal:**	
St. ate:	28-MAR-2008	**District Goal:**	13-NOV-2011
Regulatory:	12-JAN-2012		
A :	APOTEX	**Brand Name:**	DOCETAXEL INJECTION 40 MG ML
	2400 NORTH COMMERCE PKY STE 400	**Estab. Name:**	
	WESTON, FL 33326	**Generic Name:**	DOCETAXEL
Priority:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; INJECTABLE; DOCETAXEL; 20MG/.5ML 002; INJECTABLE; DOCETAXEL; 80MG/2ML	

Application Comment: SUBMISSION RESPONSE TO COMPLETE RESPONSE DATED MARCH 24, 2010- EER ENTRY DELAY DUE TO AWAITING INFORMATION FROM APPLICANT (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

COMPLETE RESPONSE RESUBMISSION DATED 07292009 (on 11-AUG-2009 by S. GOLDIE () 301-796-2055)

THIS IS A STANDARD NDA SUBMISSION. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

FDA Contacts:				
	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	J. JEE	Review Chemist		301-796-1375
	W. ADAMS	Team Leader		301-796-1321

Overall Recommendation:					
	ACCEPTABLE	on 22-AUG-2011	by D. SMITH	()	
	ACCEPTABLE	on 22-AUG-2011	by A. INYARD	()	
	PENDING	on 01-AUG-2011	by EES_PROD		
	PENDING	on 01-AUG-2011	by EES_PROD		
	ACCEPTABLE	on 28-JUL-2011	by D. SMITH	()	
	WITHHOLD	on (b) (4)	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		
	WITHHOLD	on	by EES_PROD		

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

F hment: **CFN:** 9615251 **FEI:** 3001617666

APOTEX INC

380 ELGIN MILLS RD
RICHMOND HILL, ONTARIO, CANADA

D : **AADA:**

R. .sibilities: FINISHED DOSAGE MANUFACTURER

INTERMEDIATE OTHER TESTER

Establishment Comment: THIS SITE PERFORMS MANUFACTURING, PACKAGING, LABELING, TESTING, AND STABILITY TESTING, STORAGE AND DISTRIBUTION OF DILUENT FOR THE FINAL DOSAGE FORM; PERFORMS ACCEPTANCE TESETING FOR RELEASE PURPOSES OF THE DRUG SUBSTANCES AND INACTIVE RAW MATERIALS (on 25-MAY-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	20-MAY-2010				MESMERD
OC RECOMMENDATION	(b) (4)			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	10-JAN-2011				MESMERD
SUBMITTED TO DO	12-JAN-2011	10-Day Letter			INYARDA
D RECOMMENDATION	17-JAN-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	19-JAN-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	
S TED TO OC	01-AUG-2011				MESMERD
SUBMITTED TO DO	02-AUG-2011	10-Day Letter			STOCKM
DO RECOMMENDATION	07-AUG-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	08-AUG-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

F hment: **CFN:** 9611083 **FEI:** 3002906944

APOTEX, INC.

SIGNET CAMPUS
TORONTO, ONTARIO, CANADA

D : **AADA:**

R. sibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

INTERMEDIATE OTHER TESTER

Establishment Comment: AMENDMENT DATED JANUARY 27, 2011 PROVIDES A CORRECTED COMPARISON TABLE BETWEEN EQUIPMENT AND MANUFACTURING/PACKAGING PROCESS (b) (4) PLEASE NOTE IF THESE CORRECTED EQUIPMENT AND MANUFACTURING CHANGES WER USED IN THE MANUFACTURE OF DOCETAXEL INJECTION AND THE CORRESPONDING DILUENT. (THERE WERE NO SPECIFIC FACILITIES CITED IN THIS AMENDMENT.) (on 03-AUG-2011 by A. INYARD ())

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	20-MAY-2010				MESMERD
OC RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				WARNING LETTER ISSUED	
ASSIGNED INSPECTION TO IB	15-DEC-2010	Product Specific			PHILPYE
ONCOLOGY DRUG					
IITTED TO OC	10-JAN-2011				MESMERD
SUBMITTED TO DO	12-JAN-2011	Product Specific			INYARDA
/ · ED INSPECTION TO IB	17-JAN-2011	Product Specific			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		(b) (4)
See hardcopy Establishment Inspection Report in TurboEIR.					
DO RECOMMENDATION	16-MAR-2011			WITHHOLD	PHILPYE
				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	16-MAR-2011			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	27-JUL-2011	10-Day Letter			RAMANADHAMM
DO RECOMMENDATION	28-JUL-2011			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	28-JUL-2011			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	01-AUG-2011				MESMERD
SUBMITTED TO DO	02-AUG-2011	10-Day Letter			STOCKM
O RECOMMENDATION	07-AUG-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	

OC RECOMMENDATION	08-AUG-2011	ACCEPTABLE	STOCKM
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

E ıment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

D AADA:

R sibilities: (b) (4)

Establishment Comment: (b) (4)

Profile:

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	12-AUG-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	20-MAY-2010				MESMERD
ECOMMENDATION	28-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA
SI TED TO OC	10-JAN-2011				MESMERD
OC ECOMMENDATION	09-FEB-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
SPOKE WITH D. EMERSON ON 2/9/2011 AC FOR CTL MICRO ENDO TESTING					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

F ·hment: CFN: (b) (4) (b) (4) FEI: (b) (4)

D · AADA:

R· ·sibilities: (b) (4)

Establishment Comment:

Profile:

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	17-AUG-2009	Product Specific			JOHNSONE
·ECOMMENDATION	19-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	21-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
INSP·CTION PERFORMED	(b) (4)		(b) (4)		SIMONE.PITTS

This pre-approval and product-specific GMP inspection of a control testing laboratory was conducted according to FACTS Assignment (b) (4) and in accordance with CP 7346.832 Pre-Approval Inspections and 7356.002 Drug Process Inspections. The inspection covered the Quality and Laboratory Control Systems for NDA (b) (4) . The second assignment listed was for NDA 22-312 Docetaxel, applicant holder Apotex located in Weston, FL. (b) (4) stated (b) (4) does not perform any analytical testing for this drug product at this time.

The previous inspection was conducted in (b) (4) and was classified as NAI. There were no corrective actions to review from the previous inspection.

The current inspection found (b) (4) operating as a full service contract control testing laboratory performing the analyses for stability testing of the drug substance. Product strengths covered during this inspection included (b) (4) . At the close of the inspection (b) (4), an FDA-483 was not issued, significant deviations from the cGMPs were not observed.

We instructed management final classification of the facility is at the discretion of the Center for Drug Evaluation and Research (CDER), Office of Compliance after review of the Establishment Inspection Report and relevant documentation.

No samples were collected and no refusals were encountered during the inspection. A copy of the GMP Compliance/Summary of Findings report for the firm is attached to this report.

· RECOMMENDATION	13-MAY-2010			ACCEPTABLE ADMIN CLOSURE-IGNORE RECCOMEND	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

REQUEST CANCELLED	20-MAY-2010		MESMERD
		FACILITY WITHDRAWN	
TED TO OC	11-JAN-2011		MESMERD
OC RECOMMENDATION	11-JAN-2011	ACCEPTABLE	INYARDA
		BASED ON PROFILE	
SUBMITTED TO OC	01-AUG-2011		MESMERD
OC RECOMMENDATION	02-AUG-2011	ACCEPTABLE	STOCKM
		BASED ON PROFILE	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

r y:

I. nsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING, TESTING AN DPACKAGING FOR BULK DRUG SUBSTANCE (b) (4)
THE RELATED DS DMF NUMBER HAS BEEN REVISED. THE CORRECT ONE IS DMF (b) (4) DATED 12-16-2008. (on 16-DEC-2008 by H. SARKER (HFD-150) 301-796-1747)

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

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	08-MAY-2008	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		IRIVERA
INSPECTION PERFORMED See Hard Copy Report	(b) (4)		(b) (4)		JEFFERY.HANGARTNEF
DO RECOMMENDATION	12-FEB-2009			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
OC RECOMMENDATION	12-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	14-AUG-2009			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	25-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	12-JAN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

AADA:

isibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: PERFORMS TESTING FOR DRUG PRODUCT (DOCETAXEL INJECTION) OR ITS COMPONENTS (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	28-MAY-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	12-JAN-2011			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
SUBMITTED TO OC	01-AUG-2011				MESMERD
ECOMMENDATION	02-AUG-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

AADA:

sibilities: FINISHED DOSAGE STERILIZER

Establishment Comment: (b) (4)

Profile:

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	24-AUG-2009	Product Specific			JOHNSONE
SUBMITTED TO DO	05-JAN-2010	10-Day Letter			INYARDA
ECOMMENDATION	06-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OMMENDATION	06-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	CRUZC
SUBMITTED TO OC	20-MAY-2010				MESMERD
SUBMITTED TO DO	25-MAY-2010	Product Specific			INYARDA
DO RECOMMENDATION	27-MAY-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	28-MAY-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	11-JAN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	01-AUG-2011				MESMERD
OC RECOMMENDATION	02-AUG-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22312/000	**Action Goal:**	
Stamp Date:	28-MAR-2008	**District Goal:**	16-NOV-2010
F atory:	15-MAY-2011		
Applicant:	APOTEX	**Brand Name:**	DOCETAXEL INJECTION 40 MG ML
	2400 NORTH COMMERCE PKY STE 400	**Estab. Name:**	
	WESTON, FL 33326	**Generic Name:**	DOCETAXEL
Priority:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; INJECTABLE; DOCETAXEL; 20MG/.5ML 002; INJECTABLE; DOCETAXEL; 80MG/2ML	

Application Comment: SUBMISSION RESPONSE TO COMPLETE RESPONSE DATED MARCH 24, 2010- EER ENTRY DELAY DUE TO AWAITING INFORMATION FROM APPLICANT (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

COMPLETE RESPONSE RESUBMISSION DATED 07292009 (on 11-AUG-2009 by S. GOLDIE () 301-796-2055)

THIS IS A STANDARD NDA SUBMISSION. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

FDA Contacts:				
	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	J. JEE	Review Chemist		301-796-1375
	W. ADAMS	Team Leader		301-796-1321

Overall Recommendation:					
	WITHHOLD	(b) (4)	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		
	WITHHOLD		by EES_PROD		

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9615251 **FEI:** 3001617666

APOTEX INC

380 ELGIN MILLS RD
RICHMOND HILL, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

INTERMEDIATE OTHER TESTER

Estab. Comment: THIS SITE PERFORMS MANUFACTURING, PACKAGING, LABELING, TESTING, AND STABILITY TESTING, STORAGE AND DISTRIBUTION OF DILUENT FOR THE FINAL DOSAGE FORM; PERFORMS ACCEPTANCE TESETING FOR RELEASE PURPOSES OF THE DRUG SUBSTANCES AND INACTIVE RAW MATERIALS (on 25-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	(b) (4)			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	12-JAN-2011			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	(b) (4)			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	10-JAN-2011				MESMERD
SUBMITTED TO DO	12-JAN-2011	10-Day Letter			INYARDA
DO RECOMMENDATION	17-JAN-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	19-JAN-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611083 **FEI:** 3002906944

APOTEX INC.

SIGNET CAMPUS
TORONTO, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

INTERMEDIATE OTHER TESTER

Estab. Comment:

Profile: CONTROL TESTING LABORATORY **OAI Status:** POTENTIAL OAI

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	(b) (4)			WITHHOLD WARNING LETTER ISSUED	INYARDA
SUBMITTED TO OC	10-JAN-2011				MESMERD
SUBMITTED TO DO	12-JAN-2011	10-Day Letter			INYARDA
ASSIGNED INSPECTION TO IB	17-JAN-2011	Product Specific			PHILPYE
[:COMMENDATION	(b) (4)			WITHHOLD PEND REG ACTION - WARNING LTR	PHILPYE
OC RECOMMENDATION	(b) (4)			WITHHOLD DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	(b) (4)			WITHHOLD WARNING LETTER ISSUED	INYARDA
ASSIGNED INSPECTION TO IB ONCOLOGY DRUG	15-DEC-2010	Product Specific			PHILPYE
SUBMITTED TO OC	10-JAN-2011				MESMERD
SUBMITTED TO DO	12-JAN-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	17-JAN-2011	Product Specific			PHILPYE
DO RECOMMENDATION	(b) (4)			WITHHOLD PEND REG ACTION - WARNING LTR	PHILPYE
OC RECOMMENDATION	(b) (4)			WITHHOLD DISTRICT RECOMMENDATION	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4).

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

(b) (4) TESTING OF THE DRUG SUBSTANCE AND CONCENTRATE (BULK SOLUTION AND FINISHED PRODUCT.) (on 27-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	12-AUG-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	28-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	09-FEB-2011			ACCEPTABLE BASED ON PROFILE	INYARDA
SPOKE WITH D. EMERSON ON 2/9/2011 AC FOR CTL (b) (4)					

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Estab. Comment: STERILITY TESTING OF DRUG PRODUCT CONCENTRATE AND DILUENT (on 11-JAN-2011 by D. MESMER (HFD-800) 301-796-4023)
TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	17-AUG-2009	Product Specific			JOHNSONE
DO RECOMMENDATION	19-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
C ECOMMENDATION	21-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
INSPECTION PERFORMED	(b) (4)				SIMONE.PITTS

This pre-approval and product-specific GMP inspection of a control testing laboratory was conducted according to FACTS Assignment (b) (4) and in accordance with CP 7346.832 Pre-Approval Inspections and 7356.002 Drug Process Inspections. The inspection covered the Quality and Laboratory Control Systems for NDA (b) (4) The second assignment listed was for NDA 22-312 Docetaxel, applicant holder Apotex located in Weston, FL. (b) (4) stated (b) (4) does not perform any analytical testing for this drug product at this time.

The previous inspection was conducted in (b) (4) and was classified as NAI. There were no corrective actions to review from the previous inspection.

The current inspection found (b) (4) operating as a full service contract control testing laboratory performing the analyses for stability testing of the drug substance. Product strengths covered during this inspection include (b) (4) the close of the inspection on (b) (4) an FDA-483 was not issued, significant deviations from the cGMPs were not observed.

We instructed management final classification of the facility is at the discretion of the Center for Drug Evaluation and Research (CDER), Office of Compliance after review of the Establishment Inspection Report and relevant documentation.

No samples were collected and no refusals were encountered during the inspection. A copy of the GMP Compliance/Summary of Findings report for the firm is attached to this report.

OC RECOMMENDATION	13-MAY-2010			ACCEPTABLE ADMIN CLOSURE-IGNORE RECCOMEND	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

R 'EST CANCELLED	20-MAY-2010		MESMERD
		FACILITY WITHDRAWN	
SUBMITTED TO OC	11-JAN-2011		MESMERD
OC RECOMMENDATION	11-JAN-2011	ACCEPTABLE	INYARDA
		BASED ON PROFILE	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING, TESTING AN DPACKAGING FOR BULK DRUG SUBSTANCE (b) (4)

THE RELATED DS DMF NUMBER HAS BEEN REVISED. THE CORRECT ONE IS DMF (b) (4) DATED 12-16-2008. (on 16-DEC-2008 by H. SARKER (HFD-150) 301-796-1747)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	08-MAY-2008	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	05-SEP-2008		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4) 8		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		JEFFERY.HANGARTNEF
See Hard Copy Report					
DO RECOMMENDATION	12-FEB-2009			ACCEPTABLE	ADAMSS
				ADEQUATE FIRM RESPONSE INSPECTION	
OC RECOMMENDATION	12-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	14-AUG-2009			ACCEPTABLE	STOCKM
				BASED ON PROFILE	
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	25-MAY-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	12-JAN-2011			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: PERFORMS TESTING FOR DRUG PRODUCT (DOCETAXEL INJECTION) OR ITS COMPONENTS (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-MAY-2010				MESMERD
OC RECOMMENDATION	28-MAY-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	12-JAN-2011			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILIZER

Estab. Comment: (b) (4)

Profile:

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	24-AUG-2009	Product Specific			JOHNSONE
SUBMITTED TO DO	05-JAN-2010	10-Day Letter			INYARDA
DO RECOMMENDATION	06-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	06-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	CRUZC
SUBMITTED TO OC	20-MAY-2010				MESMERD
SUBMITTED TO DO	25-MAY-2010	Product Specific			INYARDA
DO RECOMMENDATION	27-MAY-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	28-MAY-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	10-JAN-2011				MESMERD
OC RECOMMENDATION	11-JAN-2011			ACCEPTABLE BASED ON PROFILE	INYARDA

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

lication:	NDA 22312/000	**Action Goal:**	
mp Date:	28-MAR-2008	**District Goal:**	26-JUL-2010
ul :	24-SEP-2010		
licant:	APOTEX	**Brand Name:**	DOCETAXEL INJECTION 40 MG ML
	2400 NORTH COMMERCE PKY STE 400	**Estab. Name:**	
	WESTON, FL 33326	**Generic Name:**	DOCETAXEL
rity:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
. Code:	150	001; INJECTABLE; DOCETAXEL; 20MG/.5ML 002; INJECTABLE; DOCETAXEL; 80MG/2ML	

lication Comment: SUBMISSION RESPONSE TO COMPLETE RESPONSE DATED MARCH 24, 2010- EER ENTRY DELAY DUE TO AWAITING INFORMATION FROM APPLICANT (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

COMPLETE RESPONSE RESUBMISSION DATED 07292009 (on 11-AUG-2009 by S. GOLDIE () 301-796-2055)

THIS IS A STANDARD NDA SUBMISSION. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

\ Contacts:	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	J. JEE	Review Chemist		301-796-1375
	W. ADAMS	Team Leader		301-796-1321

rall Recommendation:	WITHHOLD	on 16-SEP-2010	by A. INYARD	()	
	WITHHOLD	on 29-JAN-2010	by C. CRUZ	(HFD-323)	301-796-3254
	WITHHOLD	on 08-JAN-2010	by A. INYARD	()	
	WITHHOLD	on 27-APR-2009	by A. CHARITY	(HFD-322)	301-796-3208

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** **FEI:** 3002906944

APOTEX

SIGNET CAMPUS
TORONTO, , CANADA M9L 1P3

F No: **AADA:**

ponsibilities: FINISHED DOSAGE MANUFACTURER

ab. Comment:

file: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** OAI ALERT

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				WARNING LETTER ISSUED	

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** **FEI:** 3002906944

APOTEX

3701 WESTON ROAD
TORONTO, ONTARIO, CANADA M9L 2S8

F No: **AADA:**

ponsibilities: FINISHED DOSAGE OTHER TESTER

INTERMEDIATE OTHER TESTER

ab. Comment:

file: CONTROL TESTING LABORATORY **OAI Status:** OAI ALERT

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				WARNING LETTER ISSUED	

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** 9615251 **FEI:** 3001617666

APOTEX (RICHMOND HILL)

380 ELGIN MILLS RD
RICHMOND HILL, ONTARIO, CANADA

F No: **AADA:**

ponsibilities: FINISHED DOSAGE MANUFACTURER

INTERMEDIATE OTHER TESTER

ab. Comment: THIS SITE PERFORMS MANUFACTURING, PACKAGING, LABELING, TESTING, AND STABILITY TESTING, STORAGE AND DISTRIBUTION OF DILUENT FOR THE FINAL DOSAGE FORM; PERFORMS ACCEPTANCE TESETING FOR RELEASE PURPOSES OF THE DRUG SUBSTANCES AND INACTIVE RAW MATERIALS (on 25-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

file: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
BMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	
BMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				DISTRICT RECOMMENDATION	

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

ablishment: **CFN:** 9615230 **FEI:** 3002808376

APOTEX INC ETOBICOKE SITE

50 STEINWAY BLVD
ETOBICOKE, ONTARIO, CANADA

F No: **AADA:**

ponsibilities: FINISHED DOSAGE OTHER TESTER

ab. Comment:

file: CONTROL TESTING LABORATORY **OAI Status:** OAI ALERT

istone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
BMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			WITHHOLD	INYARDA
				WARNING LETTER ISSUED	

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE OTHER TESTER

ab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

(b) (4) TESTING OF THE DRUG SUBSTANCE AND CONCENTRATE (BULK SOLUTION AND FINISHED PRODUCT.) (on 27-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

file: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
BMITTED TO OC	08-MAY-2008				SARKERH
RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS
BMITTED TO OC	11-AUG-2009				GOLDIES
RECOMMENDATION	12-AUG-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
BMITTED TO OC	20-MAY-2010				MESMERD
RF MENDATION	28-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

F No:

ponsibilities: DRUG SUBSTANCE MANUFACTURER

ab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING, TESTING AN DPACKAGING FOR BULK DRUG SUBSTANCE. (b) (4)

THE RELATED DS DMF NUMBER HAS BEEN REVISED. THE CORRECT ONE IS DMF (b) (4) DATED 12-16-2008. (on 16-DEC-2008 by H. SARKER (HFD-150) 301-796-1747)

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

stone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
BMITTED TO OC	08-MAY-2008				SARKERH
BMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
IGNED INSPECTION TO IB	08-MAY-2008	GMP Inspection			ADAMSS
PECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
PECTION PERFORMED	(b) (4)		(b) (4)		IRIVERA
PECTION PERFORMED See Hard Copy Report	(b) (4)		(b) (4)		JEFFERY.HANGARTNEF
RE MMENDATION	12-FEB-2009			ACCEPTABLE ADEQUATE FIRM RESPONSE INSPECTION	ADAMSS
RECOMMENDATION	12-FEB-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
BMITTED TO OC	11-AUG-2009				GOLDIES
RECOMMENDATION	14-AUG-2009			ACCEPTABLE BASED ON PROFILE	STOCKM
BMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	25-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE OTHER TESTER

ab. Comment: PERFORMS TESTING FOR DRUG PRODUCT (DOCETAXEL INJECTION) OR ITS COMPONENTS (on 12-MAY-2010 by D. MESMER (HFD-800) 301-796-4023)

file: CONTROL TESTING LABORATORY OAI Status: NONE

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
BMITTED TO OC	20-MAY-2010				MESMERD
RECOMMENDATION	28-MAY-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Reference ID: 3073935

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE STERILIZER

ab. Comment: (b) (4)

file:

stone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
BMITTED TO OC	08-MAY-2008				SARKERH
RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS
BMITTED TO OC	11-AUG-2009				GOLDIES
BMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
SIGNED INSPECTION TO IB	24-AUG-2009	Product Specific			JOHNSONE
BMITTED TO DO	05-JAN-2010	10-Day Letter			INYARDA
R IMENDATION	06-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
RECOMMENDATION	06-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	CRUZC
BMITTED TO OC	20-MAY-2010				MESMERD
BMITTED TO DO	25-MAY-2010	Product Specific			INYARDA
RECOMMENDATION	27-MAY-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
RECOMMENDATION	28-MAY-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22312/000	**Action Goal:**	
S Date:	28-MAR-2008	**District Goal:**	27-FEB-2009
Regulatory:	30-JAN-2010		
Applicant:	APOTEX	**Brand Name:**	DOCETAXEL INJECTION 40 MG ML
	2400 NORTH COMMERCE PKY STE 400	**Estab. Name:**	
	WESTON, FL 33326	**Generic Name:**	DOCETAXEL
Priority:	5S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; INJECTABLE; DOCETAXEL; 20MG/.5ML 002; INJECTABLE; DOCETAXEL; 80MG/2ML	

Application Comment: COMPLETE RESPONSE RESUBMISSION DATED 07292009 (on 11-AUG-2009 by S. GOLDIE () 301-796-2055)

THIS IS A STANDARD NDA SUBMISSION. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

FDA Contacts:				
	D. WOODY	Project Manager	(HFV-230)	240-276-9237
	S. CHATTERJEE	Review Chemist		301-796-2252
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:					
	WITHHOLD	on 08-JAN-2010	by A. INYARD	()	
	WITHHOLD	on 27-APR-2009	by A. CHARITY	(HFD-322)	301-796-3208

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9615251 **FEI:** 3001617666

APOTEX (RICHMOND HILL)

380 ELGIN MILLS RD
RICHMOND HILL, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING OF THE FINAL DOSAGE FORM AND TESTING. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: LARGE VOLUME PARENTERALS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
NED INSPECTION TO IB	27-AUG-2009	Product Specific			JOHNSONE
DO RECOMMENDATION	06-JAN-2010			WITHHOLD	JOHNSONE
SEE EMAIL FROM I. RIVERA 1/4/10, 5:18PM				FIRM NOT READY	
OC RECOMMENDATION	06-JAN-2010			WITHHOLD	CRUZC
				DISTRICT RECOMMENDATION	
				FIRM NOT READY	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:**

APOTEX (SIGNET CAMPUS)

285 GARYRAY DRIVE
TORONTO, ONTARIO, CANADA M9L 1P3

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING OF THE FINAL DOSAGE FORM AND TESTING. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: LARGE VOLUME PARENTERALS **OAI Status:** POTENTIAL OAI

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	27-MAY-2008	GMP Inspection			ADAMSS
OC RECOMMENDATION	27-APR-2009			WITHHOLD	CHARITYA
[redacted] (b) (4)				BASED ON FILE REVIEW DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
[COMMENDATION	17-AUG-2009			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION	30-NOV-2009			WITHHOLD	CRUZC
PEND REG ACTION - WARNING LTR				DISTRICT RECOMMENDATION	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:**

APOTEX INC (SIGNET CAMPUS)

400 ORMONT DRIVE
TORONTO, ONTARIO, CANADA M9L1N9

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. THERE IS NO CFN NUMBER FOR THE SITE. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** POTENTIAL OAI

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
I COMMENDATION	17-AUG-2009			WITHHOLD	JOHNSONE
				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	30-NOV-2009			WITHHOLD	CRUZC
PEND REG ACTION - WARNING LTR				DISTRICT RECOMMENDATION	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:**

APOTEX INC. SIGNET CAMPUS

3701 WESTON ROAD
TORONTO, ONTARIO, CANADA M9L 2S8

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. THERE IS NO CFN NUMBER FOR THE SITE. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** POTENTIAL OAI

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
:COMMENDATION	17-AUG-2009			WITHHOLD	JOHNSONE
				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	30-NOV-2009			WITHHOLD	CRUZC
PEND REG ACTION - WARNING LTR				DISTRICT RECOMMENDATION	

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	12-AUG-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 08-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	12-AUG-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	17-AUG-2009	Product Specific			JOHNSONE
DO RECOMMENDATION	19-JAN-2010			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
C COMMENDATION	21-JAN-2010			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING, TESTING AN DPACKAGING FOR BULK DRUG SUBSTANCE. THERE

THE RELATED DS DMF NUMBER HAS BEEN REVISED. THE CORRECT ONE IS DMF (b) (4) DATED 12-16-2008. (on 16-DEC-2008 by H. SARKER (HFD-150) 301-796-1747)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	08-MAY-2008	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	(b) (4)				IRIVERA
INSPECTION PERFORMED					IRIVERA
INSPECTION PERFORMED					JEFFERY.HANGARTNEF
See Hard Copy Report					
L .COMMENDATION	12-FEB-2009			ACCEPTABLE	ADAMSS
				ADEQUATE FIRM RESPONSE	
				INSPECTION	
OC RECOMMENDATION	12-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	14-AUG-2009			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	17-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	24-AUG-2009	Product Specific			JOHNSONE
INSPECTION PERFORMED	(b) (4)				DEMERSON
DO RECOMMENDATION	28-JAN-2010			WITHHOLD	JOHNSONE
(b) (4)					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	11-AUG-2009				GOLDIES
OC RECOMMENDATION	12-AUG-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Reference ID: 3073935

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILIZER

Estab. Comment: (b) (4)

Profile:

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	
SUBMITTED TO OC	11-AUG-2009				GOLDIES
SUBMITTED TO DO	14-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	24-AUG-2009	Product Specific			JOHNSONE
SUBMITTED TO DO	05-JAN-2010	10-Day Letter			INYARDA
D COMMENDATION	06-JAN-2010			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	06-JAN-2010			ACCEPTABLE	CRUZC
				DISTRICT RECOMMENDATION	

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

ication:	NDA 22312/000	Action Goal:	
Stamp:	28-MAR-2008	District Goal:	29-NOV-2008
Regulatory Due:	28-APR-2009	Brand Name:	DOCETAXEL INJECTION 40
Applicant:	APOTEX	Estab. Name:	MG ML
	2400 NORTH COMMERCE PKY STE 400	Generic Name:	DOCETAXEL
	WESTON, FL 33326		
Priority:	5S	Dosage Form:	(INJECTION)
Org Code:	150	Strength:	0.5ML AND 2ML (40MG/ML)

Application Comment: THIS IS A STANDARD NDA SUBMISSION. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

FDA Contacts:	D. WOODY	(HFV-230)	240-276-9237	, Project Manager
	S. CHATTERJEE		301-796-2252	, Review Chemist
	H. SARKER	(HFD-150)	301-796-1747	, Team Leader

Overall Recommendation: ---

Establishment: CFN 9615230 FEI 3002808376

APOTEX INC

50 STEINWAY BLVD

ETOBICOKE, ONTARIO, CA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

P le: CTX OAI Status: NONE

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. (on 07-MAY-2008

by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
ITTED TO DO	08-MAY-2008	GMP			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9615251 FEI 3001617666

APOTEX INC

380 ELGIN MILLS RD

RICHMOND HILL, ONTARIO, CA

DMF No: AADA:

P ısibilities: FINISHED DOSAGE MANUFACTURER

Profile: LVP OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING OF THE FINAL DOSAGE FORM AND TESTING. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

F lishment: CFN FEI

APOTEX INC

3701 WESTON ROAD

TORONTO, ONTARIO, CA M9L 2S8

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTX OAI Status: NONE

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. THERE IS NO CFN NUMBER FOR THE SITE. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
ITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE	ADAMSS

BASED ON FILE REVIEW

OC RECOMMENDATION 27-MAY-2008 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

Establishment: CFN FEI

APOTEX INC

285 GARYRAY DRIVE

TORONTO, ONTARIO, CA M9L 1P3

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: LVP OAI Status: NONE

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING OF THE FINAL DOSAGE FORM AND TESTING. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

stone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO DO	08-MAY-2008	GMP	ADAMSS
ASSIGNED INSPECTION T	27-MAY-2008	GMP	ADAMSS

Establishment: CFN FEI 3002906944
APOTEX INC (SIGNET CAMPUS)
150 SIGNET DRIVE
TORONTO, ONTARIO, CA

DMF No: AADA:

F nsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTX OAI Status: NONE

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: CFN FEI
APOTEX INC (SIGNET CAMPUS)
400 ORMONT DRIVE
TORONTO, ONTARIO, CA M9L1N9

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

le: CTL OAI Status: NONE

Estab. Comment: TESTING OF DRUG SUBSTANCE, DRUG PRODUCT AND EXCIPIENTS. THERE IS NO CFN NUMBER FOR THE SITE. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP			ADAMSS
DO RECOMMENDATION	27-MAY-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	27-MAY-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

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

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

[redacted] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
1ITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN [redacted] (b) (4) FEI [redacted] (b) (4)

[redacted] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

P -file: CTX OAI Status: NONE

Estab. Comment: TESTING OF DRUG PRODUCT. (on 08-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

. ɔ. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC	08-MAY-2008		SARKERH
OC RECOMMENDATION	08-MAY-2008	ACCEPTABLE	ADAMSS
		BASED ON PROFILE	

Establishment: CFN FEI (b) (4)

(b) (4)

DM To: 20961 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: THE SITE IS RESPONSIBLE FOR MANUFACTURING, TESTING AN DPACKAGING FOR BULK DRUG SUBSTANCE. (b) (4)

(b) (4)

THE RELATED DS DMF NUMBER HAS BEEN REVISED. THE CORRECT ONE IS DMF (b) (4) DATED 12-16-2008. (on 16-DEC-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
SUBMITTED TO DO	08-MAY-2008	GMP			ADAMSS
GNED INSPECTION T	08-MAY-2008	GMP			ADAMSS
INSPECTION SCHEDULED	(b) (4)				IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		IRIVERA

INSPECTION PERFORMED [redacted] [redacted] JEFFERY.HAN

See Hard Copy Report

DO RECOMMENDATION 12-FEB-2009 ACCEPTABLE ADAMSS

ADEQUATE FIRM RESPONSE

INSPECTION

OC RECOMMENDATION 12-FEB-2009 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

Establishment: CFN [redacted] FEI [redacted]

[redacted]

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: TESTING OF DRUG PRODUCT. (on 07-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

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

(b) (4)

No: AADA:

Responsibilities: (b) (4)

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

Estab. Comment: (b) (4)

08-MAY-2008 by H. SARKER (HFD-150) 301-796-1747)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-MAY-2008				SARKERH
OC RECOMMENDATION	08-MAY-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS