

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022312Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # 022312	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Docetaxel Injection (b) (4) Dosage Form: Injection Strengths: 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)		
Applicant: Apotex, Inc.		
Date of Receipt: July 12, 2011		
PDUFA Goal Date: January 12, 2012		Action Goal Date (if different):
<b>Proposed Indication(s):</b>		
<b>Breast Cancer</b> Docetaxel injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.  Docetaxel injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.		
<b>Non-Small Cell Lung Cancer</b> Docetaxel injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.  Docetaxel injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.		
<b>Prostate Cancer</b> Docetaxel injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.		
<b>Gastric Adenocarcinoma</b> Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.		
<b>Head and Neck Cancer</b> Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 020449 Taxotere (docetaxel) for Injection	Clinical, Pharm/Tox, Statistical, and Clinical Pharmacology (application only contains new CMC data)

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The Apotex Inc. drug product has a different qualitative and quantitative formulation compared to Taxotere® for both the Injection Concentrate and the Diluent. In particular, the formulation of the Apotex drug product is pharmaceutically equivalent to that of Taxotere®. However, compared to Taxotere, the Apotex formulation contains reduced amounts of alcohol and has a different excipient (polyethylene Glycol 300 NF) added to the Docetaxel Injection (b)(4). The added polyethylene glycol (b)(4) for the drug substance, and the level of this excipient is below the limit defined within the Inactive Ingredient Guide. In addition, the Apotex formulation uses Polysorbate 80 in the Diluent, whereas the RLD used Polysorbate 80 in the Injection concentrate. Based on the comparison to the RLD, ONDQA granted Apotex a waiver of the bioequivalence requirements for Docetaxel Injection® in accordance with 21 CFR 320.22 (b)(1). The waiver was granted

because the difference in excipient composition between the final dilution for injection between this product and the RLD is self evident, and is not expected to have any impact on the safety and efficacy of the drug. In the first cycle CMC review for NDA 22-312, the reviewer concurred with this biowaiver request 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 communicated to the sponsor that a clinical study in support of this application is not required.

**RELIANCE ON PUBLISHED LITERATURE**

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
*If "NO," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
*If "NO", proceed to question #5.*  
*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
*If "NO," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Taxotere (docetaxel) for Injection	NDA 020449	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES  NO

*If "YES", please list which drug(s) and answer question d) i. below.*

*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a different qualitative and quantitative formulation for both the Injection (b)(4) and the diluent, different excipients in the concentrate product and use of Polysorbate 80 in the diluent.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If “NO” to (a) proceed to question #11.  
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If “YES” to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “NO” **or** if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do **not** have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):  
NDA 020449 Taxotere (docetaxel injection)  
NDA 022534 Docetaxel Injection  
NDA 022234 Docetaxel Injection  
NDA 201195 Docetaxel Injection  
NDA 201525 Docetaxel Injection

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

<b>PATENT CERTIFICATION/STATEMENTS</b>
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12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5698582, 5698582\*PED, 5714512,  
5714512\*PED, 5750561, 5750561\*PED

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 4814470

Expiry date(s): 11/14/10

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5698582, 5714512, 5750561

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *June 30, 2008*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTY L COTTRELL  
01/11/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 21, 2011

To: Robert Justice, MD, Director  
Division of Oncology Products 1

Through: Todd Bridges, RPh, Team Leader  
Irene Z Chan, PharmD, BCPS, Team Leader  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: James Schlick, RPh, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Docetaxel Injection  
20 mg/0.5 mL and 80 mg/2 mL

Application Type/Number: NDA 022312

Applicant: Apotex Inc.

OSE RCM #: 2011-2791

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

# 1 INTRODUCTION

This review evaluates the revised labels and labeling for Apotex's Docetaxel Injection for areas of vulnerability that can lead to medication errors. This review is written in response to a request from the Division of Oncology Products 1. The revised labels and labeling submitted on November 3, 2011 are in response to OSE Review 2010-1346, dated April 5, 2011.

## 1.1 REGULATORY HISTORY

This NDA is a 505(b) (2) application. The Reference Listed Drug is 2-vial Taxotere (Docetaxel) Injection Concentrate, NDA 020449. DMEPA reviewed the labels and labeling for this NDA in OSE Review 2008-836, dated February 27, 2009 and our comments were communicated in the Complete Response (CR) letter dated April 28, 2009. Subsequently, revised labels and labeling were submitted by the Applicant on July 29, 2009, in their submission in response to the CR action. These revised labels and labeling were reviewed in OSE Review 2009-1868, dated January 26, 2010. The application received another CR action on January 29, 2010; however, our label and labeling recommendations from OSE Review 2009-1868 were not forwarded to the Applicant. The Applicant submitted a Class 2 Resubmission on March 24, 2010; however, another CR action was taken on September 22, 2010. Our label and labeling comments from OSE Review 2009-1868 were provided in that CR letter. Subsequently, the Applicant submitted a Class 2 Resubmission on November 12, 2010 which contained revised labels and labeling. These revised labels and labeling were reviewed in OSE Review 2010-1346, dated April 5, 2011. The application received another CR action on May 4, 2011. However, our label and labeling recommendations from OSE Review 2010-1346 were not forwarded to the Applicant. The Applicant submitted another Class 2 Resubmission on July 12, 2011. The revised labels and labeling submitted on November 3, 2011 are in response to OSE Review 2010-1346, dated April 5, 2011.

## 1.2 BACKGROUND ON DOCETAXEL PRODUCTS

Taxotere, a Sanofi Aventis product, was approved on May 14, 1996. It is a two-vial configuration consisting of one vial of active drug solution (40 mg/mL) and one vial of diluent that must be mixed together to yield a concentration of 10 mg/mL before being added to the infusion solution. The two-vial configuration has undergone numerous label and labeling changes in addition to educational interventions to address medication errors that resulted from confusion with the unusual two-step dilution.

On August 2, 2010, a new one-vial formulation of Taxotere was approved by the FDA. This one-vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one-vial formulation was approved with a concentration of 20 mg/mL.

On March 8, 2011, a 505(b)(2) application for Docetaxel Injection manufactured by Hospira was approved by the FDA. On June 29, 2011, another 505 (b)(2) application for Docetaxel Injection manufactured by Sandoz was approved by the FDA. The Docetaxel Injection products by Hospira and Sandoz are also one-vial formulations like the one-vial formulation of Taxotere. An important difference between these two products as compared to the one vial Taxotere formulation by Sanofi Aventis is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's and Sandoz's one-vial formulations are available in a concentration of 10 mg/mL.

(b) (4)

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(b) (4) Since approval, we have received complaints concerning this disparity in concentrations.

Although (b) (4) a one-vial Taxotere formulation has been introduced to the market, an additional product like the two-vial Taxotere was approved by the FDA. This application, submitted by Accord Healthcare, was approved on June 8, 2011 as a 505 (b)(2) application. Accord Healthcare's Docetaxel Injection is a two-vial formulation that yields a 10 mg/mL concentration after the initial reconstitution step, the same as the two-vial Taxotere by Sanofi Aventis. The proposed Apotex Docetaxel Injection evaluated in this review is also a two-vial formulation, like the two-vial Taxotere.

Lastly, the FDA approved a 505 (b)(2) application, submitted by Sun Pharma Global as a powder for injection, which differentiates it from all the other approved and pending docetaxel products. Appendix A summarizes the approved and pending docetaxel injection products.

### **1.3 PRODUCT INFORMATION FOR APOTEX'S DOCETAXEL INJECTION**

Apotex's Docetaxel Injection is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Docetaxel Injection has a boxed warning concerning toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. The dosing regimens vary depending on the indication of use (see Appendix B).

Apotex's Docetaxel Injection is a two-vial formulation which will be available in 20 mg/0.5 mL and 80 mg/2 mL strengths. It must be diluted with the supplied diluent to yield a concentration of 10 mg/mL, the same as the Reference Listed Drug – two-vial Taxotere by Sanofi Aventis. The required amount is withdrawn from the vial(s) and must be further diluted by adding it to the to either a 5% dextrose solution or a 0.9% sodium chloride solution. Docetaxel Injection diluted solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered intravenously through polyethylene-lined administration sets over one hour. The inactive ingredients in the active drug and diluent differ from those in the RLD.

## **2 METHODS AND MATERIALS**

DMEPA previously conducted an AERS search to identify medication errors involving Taxotere or docetaxel on March 21, 2011(see OSE review 2010-2465 dated, April 5, 2011). Given the number of approved docetaxel products, pending applications, and complicated safety issues concerning these products, DMEPA conducted a new search of the FDA Adverse Event Reporting System (AERS) database. The container labels, carton labeling, and insert labeling were reviewed as well.

### **2.1 AERS SELECTION OF MEDICATION ERROR CASES**

An AERS search was conducted on October 20, 2011 using the MedDRA High Level Group Term "Medication Errors", High Level Term "Product Label Issues", and Preferred Term "Product Quality Issues", active ingredient "Docetaxel", trade name "Taxotere", and verbatim "Taxot%" and "Doce%". The search was limited to the dates March 22, 2011 through October 20, 2011. This time period covers the time since our last AERS search was conducted in OSE Review 2010-2465. The results of the AERS search can be found in OSE review 2011-2624, dated December 21, 2011.

### **2.2 LABEL AND LABELING RISK ASSESSMENT**

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels and carton and insert labeling. This review summarizes our evaluation of the following labels and labeling (see Appendices C through E).

- Container Labels (active drug): 20mg/0.5 mL and 80 mg/2 mL (submitted November 3, 2011)
- Diluent Container Labels: for the 20 mg and 80 mg active drug vials (submitted November 3, 2011)
- Carton Labeling: 20mg/0.5 mL and 80 mg/2 mL (submitted November 3, 2011)
- Insert Labeling: No image (submitted July 12, 2011)

### 3 RESULTS

#### LABEL AND LABELING RISK ASSESSMENT

The Applicant implemented all previous recommendations in OSE Review 2010-1346, dated April 5, 2011. However, after additional analysis, the blue line underneath the statement “Before Initial Dilution\*” on the principle display panels of the carton labeling should be moved to between the statements “ \* see side panel for concentration obtained after initial dilution step” and “FOR INTRAVENOUS INFUSION ONLY AFTER FINAL DILUTION”. Additionally, the statement “ \*see side panel for...” should have the corresponding background color used to highlight the strength incorporated behind it as well. These changes increase the prominence of the statement and ensure the product is prepared correctly.

#### 4 RECOMMENDATIONS

Our evaluation identified areas where information on the carton labeling can be improved to minimize the potential for medication errors. The most recently approved Taxotere labels and labeling for the two-vial formulation (see Appendices F through I) reflect DMEPA’s most recent recommendations for minimizing the risk of medication errors. Thus, we believe the proposed labels and labeling should be consistent with the labels and labeling of the two-vial Taxotere. Section 4.1, *Comments to the Applicant*, contains our recommendations for the carton labeling. These recommendations may be incorporated into the carton labeling at the next printing.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact OSE Safety Regulatory Project Manager, Mark Liberatore, at 301-796-2221.

#### 4.1 COMMENTS TO THE APPLICANT

##### A. Carton Labeling

1. Relocate the thick blue line underneath the statement “Before Initial Dilution\*” to between the statements “ \*see side panel for concentration obtained after initial dilution step” and “FOR INTRAVENOUS INFUSION ONLY AFTER FINAL DILUTION”.
2. Incorporate the same background color used to highlight the strength behind the statement “ \* see side panel for...” to create one whole color block.

## REFERENCES

Schlick, James. Docetaxel Injection Labeling Review, OSE Review 2011-2624, dated December 21, 2011.

Holmes, Loretta. Docetaxel Injection Labeling Review, OSE Review 2010-1346, dated April 6, 2011

## APPENDICES

### Appendix A: Table of Docetaxel Injection Products

<b>NDA</b>	<b>Applicant</b>	<b>Formulation</b>	<b>Concentration</b>	<b>Status</b>
20449/S-054 Taxotere	Sanofi-Aventis	1 vial	20 mg/mL	Approved
20449 Taxotere	Sanofi-Aventis	2 vial	10 mg/mL after initial dilution	Approved
201195	Accord Healthcare	2 vial	10 mg/mL after initial dilution	Approved
022234	Hospira	1 vial	10 mg/mL	Approved
201525	Sandoz	1 vial	10 mg/mL	Approved
022534 Docefrez	Sun Pharma Global FZE	Lyophilized powder plus diluent	<b>20 mg vial</b> 20 mg/0.8 mL (25 mg/mL) <b>80 mg vial</b> 24 mg/mL	Approved
(b) (4)				
022312	Apotex	2 vial	10 mg/mL after initial dilution	Pending

**Appendix B: Docetaxel Injection Indications of Use and Dosage Information**

Indication of Use	Dosage
Breast cancer: locally advanced or metastatic	60 mg to 100 mg/m <sup>2</sup> single agent
Breast cancer adjuvant	75 mg/m <sup>2</sup> administered 1 hour after doxorubicin 50 mg/m <sup>2</sup> and cyclophosphamide 500 mg/m <sup>2</sup> every 3 weeks for 6 cycles
Non-small cell lung cancer, after platinum therapy failure	75 mg/m <sup>2</sup> single agent
Non-small cell lung cancer, chemotherapy naïve	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup>
Hormone refractory prostate cancer	75 mg/m <sup>2</sup> with 5 mg prednisone twice a day continuously
Gastric adenocarcinoma	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup> (both on day 1 only) followed by fluorouracil 750 mg/m <sup>2</sup> per day as a 24-hr intravenous infusion (days 1-5), starting at end of cisplatin infusion
Squamous cell carcinoma of the head and neck	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup> intravenously (day 1), followed by fluorouracil 750 mg/m <sup>2</sup> per day as a 24-hour intravenous infusion (days 1-5), starting at end of cisplatin infusion; for 4 cycles
Squamous cell carcinoma of the head and neck	75 mg/m <sup>2</sup> followed by cisplatin 100 mg/m <sup>2</sup> intravenously (day 1), followed by fluorouracil 1000 mg/m <sup>2</sup> per day as a 24-hour intravenous infusion (days 1-4); for 3 cycles
<b>Premedication Regimen</b>	<p>Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before administration.</p> <p>Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12 hours, 3 hours, and 1 hour before treatment</p>

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES H SCHLICK  
12/21/2011

TODD D BRIDGES  
12/21/2011

IRENE Z CHAN  
12/21/2011

CAROL A HOLQUIST  
12/21/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 5, 2011

To: Robert Justice, MD, Director  
Division of Drug Oncology Products

Through: Irene Z. Chan, PharmD, BCPS, Team Leader  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Docetaxel Injection  
20 mg/0.5 mL and 80 mg/2 mL

Application Type/Number: NDA 022312

Applicant: Apotex Inc.

OSE RCM #: 2010-1346

## 1 INTRODUCTION

This review evaluates the labels and labeling for Apotex's Docetaxel Injection submitted on November 12, 2010 for areas of vulnerability that can lead to medication errors. This review is written in response to a request from the Division of Drug Oncology Products.

### 1.1 REGULATORY HISTORY

This NDA is a 505(b)(2) application. The Reference Listed Drug is Taxotere (Docetaxel) Injection Concentrate, NDA 020449.

DMEPA reviewed the labels and labeling for this NDA in OSE Review 2008-836, dated February 27, 2009 and our comments were communicated in the Complete Response (CR) letter dated April 28, 2009. Subsequently, revised labels and labeling were submitted by the Applicant on July 29, 2009, in their submission in response to the CR action. These revised labels and labeling were reviewed in OSE Review 2009-1868, dated January 26, 2010. The application received another CR action on January 29, 2010; however, our label and labeling recommendations from OSE Review 2009-1868 were not forwarded to the Applicant. The Applicant submitted a Class 2 Resubmission on March 24, 2010; however, another CR action was taken on September 22, 2010. Our label and labeling comments from OSE Review 2009-1868 were provided in that CR letter. Subsequently, the Applicant submitted a Class 2 Resubmission on November 12, 2010 which contained revised labels and labeling that are the subject of this review.

### 1.2 BACKGROUND ON DOCETAXEL PRODUCTS

Taxotere, a Sanofi Aventis product, was approved on May 14, 1996, as a two-vial configuration consisting of one vial of active drug solution (40 mg/mL) and one vial of diluent that must be mixed together to yield a concentration of 10 mg/mL before being added to the infusion solution. The two-vial configuration has undergone numerous label and labeling changes in addition to educational interventions to address medication errors that resulted from confusion with the unusual two-step dilution.

On August 2, 2010, a new one-vial formulation of Taxotere was approved by the FDA. This one-vial formulation does not require a two step dilution process, and the drug can be withdrawn from the vial and added directly to the infusion solution. However, whereas the two-vial formulation yielded a concentration of 10 mg/mL before being added to the infusion solution, the new one-vial formulation was approved with a concentration of 20 mg/mL.

On March 8, 2011, a 505(b)(2) application for Docetaxel Injection, manufactured by Hospira, was approved by the FDA. The Docetaxel Injection by Hospira is also a one-vial formulation like the one-vial formulation of Taxotere. An important difference between these two products is their concentration. Taxotere's one-vial formulation is available in a concentration of 20 mg/mL, whereas Hospira's one-vial formulation of docetaxel is available in a concentration of 10 mg/mL. The reference listed drug for Hospira's product is Taxotere. Since approval, we have received complaints concerning this disparity in concentrations.

(b) (4)  
(b) (4) including this one,  
which propose a two-vial formulation of docetaxel. These two-vial formulations will yield a 10 mg/mL concentration after the initial reconstitution step which is the same as two-vial Taxotere. (b) (4)

### 1.3 PRODUCT INFORMATION FOR APOTEX'S DOCETAXEL INJECTION

Docetaxel Injection is indicated for the treatment of breast cancer, non-small cell lung cancer and hormone refractory prostate cancer. Docetaxel Injection has a boxed warning concerning toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. The dosing regimens vary depending on the indication of use (see Appendix A).

Docetaxel Injection is a two-vial formulation which will be available in 20 mg/0.5 mL and 80 mg/2 mL strengths which must be diluted with the supplied diluent to yield a concentration of 10 mg/mL. The required amount is withdrawn from the vial(s) and must be further diluted by adding it to the infusion solution. Docetaxel Injection diluted solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered intravenously through polyethylene-lined administration sets over one hour. The active drug plus diluent will be packaged in a blister pack in one carton. The inactive ingredients in the active drug and diluent differ from those in the RLD.

## 2 METHODS AND MATERIALS

DMEPA previously conducted an AERS search to identify medication errors involving Taxotere or docetaxel (see OSE review 2007-548 dated March 23, 2007). Results of the previous search were used to inform label and labeling recommendations for Taxotere two-vial formulation in order to minimize medication errors that were occurring at that time. Since 2007, an updated search for docetaxel medication errors has not been completed. Given the changes to the labels and labeling for Taxotere since 2007, the multiple pending applications, and complicated safety issues concerning docetaxel products, DMEPA conducted a new search of the FDA Adverse Event Reporting System (AERS) database. We also reviewed a medication error report from the Institute for Safe Medication Practices (ISMP). The proposed labels and labeling were reviewed as well.

### 2.1 AERS SELECTION OF MEDICATION ERROR CASES

An AERS search was conducted on March 21, 2011 using the MedDRA High Level Group Terms "Medication Errors" and "Product Quality Issues", active ingredient "Doce%", trade name "Taxo%", and verbatim "Taxo%" and "Doce%". The search was limited to the dates March 23, 2007 through March 21, 2011. This time period covers the time since our last AERS search conducted for OSE Review 2007-548.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If the root cause(s) could be associated with the labels, labeling, or packaging of the product, the cases were considered pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse drug event not resulting from a medication error, product quality complaints, etc.), were excluded from further analysis.

## 2.2 ISMP MEDICATION ERROR REPORT

The article “Dosing error with the new Taxotere concentration” in the March 24, 2011 issue of ISMP Medication Safety Alert<sup>1</sup> was reviewed.

## 2.3 LABEL AND LABELING RISK ASSESSMENT

DMEPA used Failure Mode and Effects Analysis (FMEA) to evaluate the container labels and carton labeling submitted on November 12, 2010 (see Appendices D and E).

- Container Labels (active drug): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent Container Labels: for the 20 mg and 80 mg active drug vials
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL

## 3 RESULTS AND DISCUSSION

The following sections describe the findings and assessment of the AERS data, ISMP medication error report, and the label and labeling review.

### 3.1 FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES

The AERS search conducted on March 21, 2011, retrieved 26 cases (see Appendix B for ISR numbers). Of the 26 cases, 23 were excluded (see Appendix C). Thus, three reports remained for our evaluation:

Potential Error (n=2)

- The reporter stated the product packaging of Taxotere is confusing because the 80 mg/2 mL active drug plus the 7.1 mL of diluent adds up to 9.1 mL, not the 80 mg/8 mL needed for a 10 mg/mL concentration. The reporter further explained that this could lead to errors if a person didn’t closely read the entire box prior to final product preparation. (ISR #5581415)
- The reporter stated the concentration of the new Taxotere [one-vial] formulation (20 mg/mL) could cause an overdose because this is an increase from the two-vial Taxotere which is 10 mg/mL after the initial dilution step. (ISR #7092480)

Improper Dose or Wrong Technique (n=1)

- The reporter stated students made 3 doses of Taxotere incorrectly, all of which were caught prior to patient administration. The details of the error were not reported; therefore, it is difficult to determine whether an improper dose was made or if wrong technique was used in preparing the doses (ISR # 5403737).

Our AERS results indicate there is still confusion with the two-vial formulation of Taxotere between the concentration of the active drug vial and the resultant concentration after the initial dilution step. The concentration of the active drug is necessary on the vial label in order to inform healthcare practitioners of its contents. Additionally, it is due to the physical characteristics of the product that the volume of active drug plus the volume of diluent, when they are combined, do not add up to the expected volume. This is explained in the insert labeling, and it is not feasible to put all of this additional information on the container labels and carton

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<sup>1</sup> “Dosing error with new Taxotere concentration,” *ISMP Medication Safety Alert*, Vol. 16, Issue 6, March 24, 2011.

labeling due to space limitations. However, the instructions for preparation are highlighted on the container labels and carton labeling so that they are readily available and if they are read, the product can be prepared correctly. We will ensure this is included for the container labels and carton labeling for Docetaxel Injection.

DMEPA is aware that the Taxotere one-vial formulation (20 mg/mL), approved on August 2, 2010, may cause confusion that can lead to medication errors due to differences in concentration and preparation instructions from the two-vial formulation. Additionally, Hospira's one-vial formulation for Docetaxel Injection (10 mg/mL) compounds the confusion because its concentration is different from one-vial Taxotere. We make recommendations in section 4 below based on previous recommendations implemented for Taxotere two-vial formulation to minimize the risk of confusion.

### **3.2 ISMP MEDICATION ERROR REPORT**

ISMP published a report dated March 24, 2011, that described a medication error in which a patient on Taxotere received twice the intended dose 100 mg/m<sup>2</sup> rather than the reduced dose of 50 mg/m<sup>2</sup>. This error occurred soon after an ambulatory cancer center pharmacy began to transition from the two-vial Taxotere which yields a concentration of 10 mg/mL after initial dilution to the new one-vial Taxotere which has a 20 mg/mL concentration. The physician ordered 50 mg/m<sup>2</sup> and although the dose administered was 100 mg/m<sup>2</sup> which is within safe dosing limits, the patient suffered febrile neutropenia which necessitated hospitalization. There are a number of factors that could lead to such an error including long-time familiarity with the two-vial Taxotere formulation, confirmation bias, delays in updating computer software to reflect the new concentration, stocking of both products concurrently, calculating the dose based on the 10 mg/mL concentration but using the 20 mg/mL concentration to prepare the infusion, and lack of knowledge regarding the new concentration of Taxotere.

### **3.3 LABEL AND LABELING RISK ASSESSMENT**

The following deficiencies were noted in the container labels and/or carton labeling:

- The black print used [REDACTED] (b) (4) is difficult to read.
- The caution statement presentation is not the same as that used for two-vial Taxotere.
- The "Rx Only" statement is too prominent.

Due to the availability of multiple formulations in varying concentrations that require differing instructions for drug preparation, the potential for confusion among these products is a significant safety concern for DMEPA. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized.

We provide recommendations that we believe will help to minimize the potential for confusion between the varying formulations, concentrations, and preparation instructions among the different docetaxel products in section 4 below.

## **4 RECOMMENDATIONS**

Our evaluation identified areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. The most recently approved Taxotere labels and labeling for the two-vial formulation (see Appendices F through I) reflect DMEPA's most recent recommendations for minimizing the risk of medication errors. Thus, we believe the proposed labels and labeling should be consistent with the labels and labeling of the two-vial Taxotere. Section 4.1, *Comments to the Applicant*, contains our recommendations for

the container labels and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

#### 4.1 COMMENTS TO THE APPLICANT

- A. General Comment for the Active Drug Labels and Carton Labeling (20 mg/0.5 mL and 80 mg/2 mL)

The established name is difficult to read (b) (4)  
[REDACTED]  
[REDACTED] We recommend you (b) (4) in order to improve the visibility of the established name.

- B. Container Labels (20 mg/0.5 mL and 80 mg/2 mL)

Box the caution statement.

- C. Blister Labeling (20 mg/0.5 mL and 80 mg/2 mL)

See comment B above.

- D. Diluent Labeling

Place the following in the caution statement in bold font: “**1.8 mL**” and “**7.1 mL**”

- E. Carton Labeling (20 mg/0.5 mL and 80 mg/2 mL)

1. Decrease the size of the “Rx Only” statement and relocate it to a position below the “FOR INTRAVENOUS INFUSION...” statement. Reposition the statements “\*see side panel...” and “FOR INTRAVENOUS INFUSION...” higher up on the principal display panel and below the dark blue line.
2. Revise the statement (b) (4) to read “Single Use Vials”

**REFERENCES**

Holmes, Loretta. Docetaxel Injection (b) (4) Label and Labeling Review, OSE Review 2008-836, dated February 27, 2009.

Holmes, Loretta. Docetaxel Injection (b) (4) Label and Labeling Review, OSE Review 2009-1868, dated January 26, 2010.

**APPENDICES**

**Appendix A: Docetaxel Injection Indications of Use and Dosage Information**

Indication of Use	Dosage
Breast cancer: locally advanced or metastatic	60 mg to 100 mg/m <sup>2</sup> single agent
Breast cancer adjuvant	75 mg/m <sup>2</sup> administered 1 hour after doxorubicin 50 mg/m <sup>2</sup> and cyclophosphamide 500 mg/m <sup>2</sup> every 3 weeks for 6 cycles
Non-small cell lung cancer, after platinum therapy failure	75 mg/m <sup>2</sup> single agent
Non-small cell lung cancer, chemotherapy naïve	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup>
Hormone refractory prostate cancer	75 mg/m <sup>2</sup> with 5 mg prednisone twice a day continuously
<b>Premedication Regimen</b>	Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before administration.  Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12 hours, 3 hours, and 1 hour before treatment

**Appendix B: AERS Database ISR Report Numbers**

Report	ISR Number
1	5316842
2	5338548
3	5403737
4	5455743
5	5490684
6	5581415
7	5621594
8	5684161
9	5744074
10	5788965
11	6082771
12	6134156
13	6221946
14	6392206
15	6607952
16	6611878
17	6673107
18	7033529
19	7092480
20	7153486
21	7206114
22	7206129
23	7206142
24	7235796
25	7241888
26	7270819
27	7355206

**Appendix C:** Excluded AERS Search Results

The AERS search conducted on March 21, 2011 yielded 26 cases. Of these cases, 23 were excluded from further evaluation for the reasons below:

- Adverse drug reactions not related to a medication error (n=11)
- Taxotere was a concomitant medication and not involved in a medication error (n=6)
- Cases reported both an adverse drug reaction not related to a medication error and product quality complaint (n=4)
- Wrong route of administration. Foreign case (Germany). There was not enough information provided to evaluate the case. (n=1)
- Improper dose (overdose). The patient was in a study protocol and there was not enough information provided to evaluate the case. (n=1)

**Appendix D:** Container Labels (Active Drug and Diluent)

Active Drug



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IRENE Z CHAN on behalf of LORETTA HOLMES  
04/05/2011

IRENE Z CHAN  
04/05/2011

CAROL A HOLQUIST  
04/06/2011



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/s/  
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JEANINE A BEST  
08/31/2010

HARI C SACHS  
08/31/2010

I agree with the recommendations in this consult (b) (4)

LISA L MATHIS  
09/07/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 26, 2010

To: Robert Justice, MD, Director  
Division of Drug Oncology Products

Through: Kristina C. Arnwine, PharmD, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Docetaxel Injection (b) (4)  
20 mg/0.5 mL and 80 mg/2 mL  
(40 mg/mL)

Application Type/Number: NDA 022312

Applicant: Apotex Inc.

OSE RCM #: 2009-1868

## 1 INTRODUCTION

This review was written in response to a request from the Division of Drug Oncology Products (HFD-150) for assessment of the revised labels and labeling of Docetaxel Injection (b) (4) (NDA 22312).

DMEPA previously reviewed labels and labeling for this product in OSE Review 2008-836, dated February 27, 2009. The application received a complete response action on April 28, 2009. Subsequently, revised labels and labeling were submitted by the Applicant on July 29, 2009, in their submission in response to the complete response action.

## 2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the revised container labels, carton and insert labeling submitted as part of the July 29, 2009 submission (see Appendix A and B).

- Container Labels (active drug): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent container labels for the 20 mg and 80 mg active drug vials
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL
- Insert Labeling (no image)
- DMEPA's previous label and labeling review for this NDA (OSE Review 2008-836, dated February 27, 2009).

## 3 RECOMMENDATIONS

The Applicant addressed all of the recommendations from our previous review, however, we have identified additional areas that need improvement. Section 3.1 *Comments to the Applicant* contains our recommendations for the revised container labels and carton labeling. We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sarah Simon, at 301-796-5205.

### 3.1 COMMENTS TO THE APPLICANT

#### A. Container Labels

##### 1. 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.

2. 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.

B. Carton Labeling

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

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

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LORETTA HOLMES  
01/26/2010

KRISTINA C ARNWINE  
01/26/2010

DENISE P TOYER  
01/26/2010

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 22-312	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Docetaxel Injection Dosage Form: Injection Strengths: 40 mg/mL		
Applicant: Apotex, Inc.		
Date of Receipt: March 28, 2008		
PDUFA Goal Date: April 28, 2009		Action Goal Date (if different):
Proposed Indication(s): <b>Breast Cancer (BC):</b> single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC  <b>Non-Small Cell Lung Cancer (NSCLC):</b> single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC  <b>Hormone Refractory Prostate Cancer (HRPC):</b> with prednisone in androgen independent (hormone refractory) metastatic prostate cancer		

**GENERAL INFORMATION**

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If “YES,” proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES  NO

*If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20-449 Taxotere (docetaxel) for Injection	Clinical, Pharm/Tox, Statistical, and Clinical Pharmacology data (application only contains new CMC data)

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

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. In the CMC review for NDA 22-312, the reviewer concurred with this biowaiver request 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 communicated to the sponsor that a clinical study in support of this application is not required.

**RELIANCE ON PUBLISHED LITERATURE**

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #6.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO”, proceed to question #6*

If "YES", list the listed drug(s) identified by name and answer question #5(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO

**RELIANCE ON LISTED DRUG(S)**

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?  
YES  NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Taxotere (docetaxel) for Injection	NDA 20-449	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
YES  NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:  
a. Approved in a 505(b)(2) application?  
YES  NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b. Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c. Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES  NO

*If "YES", please list which drug(s) and answer question d.1.*

*If "NO", proceed to question #10.*

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a different qualitative and quantitative formulation for both the Injection Concentration and the diluent, different excipients in the concentrate product and use of Polysorbate 80 in the diluent.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable*

standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES  NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): NDA 20-449 for Taxotere (sanofi-aventis) [innovator product, RLD]; NDA 22-234 for Docetaxel Injection (Hospira) [505(b)(2) application with Tentative Approval]

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES  NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

### PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): NDA 20-449  
Patent numbers: 4814470, 5438072, 5698582, 5714512, 5750561

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES  NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an “old antibiotic” (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 4814470

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s): 5438072, 5698582, 5714512, and 5750561

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received: June 30, 2008

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21

CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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this page is the manifestation of the electronic signature.**  
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/s/

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Christy Cottrell  
4/23/2009 02:38:41 PM  
CSO

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-312 Supplement # Efficacy Supplement Type SE-

Proprietary Name: N/A  
Established Name: docetaxel  
Strengths: 40mg/mL

Applicant: Apotex, Inc.  
Agent for Applicant (if applicable): Kiran Krishnan=US Agent

Date of Application: 3-27-08  
Date of Receipt: 3-31-08  
Date clock started after UN: N/A  
Date of Filing Meeting: 5-21-08  
Filing Date: 5-30-08  
Action Goal Date (optional):

User Fee Goal Date: Major amendment  
extended to 4-28-09

Indication(s) requested:

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.

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 5  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the

*User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic  Combined paper + eNDA

This application is in: NDA format  CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 78,376

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) Sept 27, 2007 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
 If no, did applicant submit a complete environmental assessment? YES  NO   
 If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: May 21, 2008

NDA #: 22-312

DRUG NAMES: Docetaxel Injection

APPLICANT: Apotex, Inc

BACKGROUND: Submitted as 505b2 with Taxotere as RLD.

ATTENDEES: Alice Kacuba, CPMS; Dillard Woody, RPM; Robert Justice, DD, Ramzi Dagher, DDD, Amna Ibrahim, MOTL, Qin Ryan, MO; Hari Sarker, CMC; Sharmista Chatterjee, CMC; Jeanie Fourie, Clin Pharm; Margaret Brower, PT; Haleh Saber, PT TL

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

**Reviewer**

Medical:	Qin Ryan
Secondary Medical:	Amna Ibrahim
Statistical:	N/A
Pharmacology:	Margaret Brower
Statistical Pharmacology:	Haleh Saber
Chemistry:	Sarmista Chatterjee
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Jeanie Fourie
Microbiology, sterility:	S. Langulle
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
OPS:	N/A
Regulatory Project Management:	Dillard Woody
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
 If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site audit(s) needed?	YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
If no, explain:				
• Advisory Committee Meeting needed?	YES, date if known	_____	NO	<input checked="" type="checkbox"/>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	N/A	<input checked="" type="checkbox"/>	YES	<input type="checkbox"/>
			NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>
			REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>
			REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	<input checked="" type="checkbox"/>
			REFUSE TO FILE	<input type="checkbox"/>
• Biopharm. study site audits(s) needed?	YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>
			REFUSE TO FILE	<input type="checkbox"/>
• GLP audit needed?	YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
CHEMISTRY			FILE	<input checked="" type="checkbox"/>
			REFUSE TO FILE	<input type="checkbox"/>
• Establishment(s) ready for inspection?	YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Sterile product?	YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?	YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:  
Any comments: n/A

REGULATORY CONCLUSIONS/DEFICIENCIES:  
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center

Director) or denying (for signature by ODE Director) an exception for review.

4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Alice Kacuba  
Regulatory Project Manager

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/s/

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Alice Kacuba  
4/21/2009 06:54:54 PM  
CSO

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**Memorandum: Internal Labeling Consult**

**Date:** April 15, 2009

**To:** Christy Cottrell, DDOP Project Manager

**From:** Keith Olin, Regulatory Reviewer  
Division of Drug Marketing, Advertising, and Communications

**Subject:** NDA 22-312  
DDMAC labeling comments for Docetaxel Injection, IV

---

DDMAC has reviewed the proposed PI for Docetaxel and offered comments for this NDA. The following comment was addressed in the label dated March 10, 2009 for Docetaxel. Note: DDMAC also offered comments during the labeling meetings.



(b) (4)

1 Page of Draft Labeling Withheld in Full as b4  
(CCI/TS) immediately following this page

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/s/  
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Keith Olin  
4/15/2009 05:06:40 PM  
DDMAC PROFESSIONAL REVIEWER



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: February 27, 2009

To: Robert Justice, MD, Director  
Division of Drug Oncology Products

Thru: Kristina C. Arnwine, PharmD, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Docetaxel Injection (b) (4)  
20 mg/0.5 mL and 80 mg/2 mL  
(40 mg/mL)

Application Number: NDA 22-312

Applicant: Apotex Inc.

OSE RCM #: 2008-836

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## EXECUTIVE SUMMARY

Our Label and Labeling Comparative Analysis and Label and Labeling Risk Assessment noted important areas (e.g., the Caution Statement wording) where the labels/labeling of Docetaxel Injection (b) (4) differ from those of Taxotere Injection Concentrate, the reference listed drug (RLD). This is a safety concern because the Taxotere labels/labeling have undergone several revisions over the years in order to address medication error reports concerning drug preparation errors. These errors were due to confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. We believe the current Taxotere labels/labeling are better designed as a result of the revisions they have undergone. Having the proposed Docetaxel Injection reflect those changes in specific areas will also make for better designed labels/labeling of Docetaxel Injection as well. The Division of Medication Error Prevention and Analysis provides recommendations in Section 6 of this review.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review was written in response to a request from the Division of Drug Oncology Products (HFD-150) for assessment of the labels and labeling of Docetaxel Injection (b) (4)

### 1.2 REGULATORY HISTORY

This NDA for Docetaxel Injection (b) (4) is a 505(b)(2) application and the reference listed drug is Taxotere (Docetaxel) Injection Concentrate (NDA 20-449). The active drug and diluent formulations of Docetaxel Injection (b) (4) differ from those of Taxotere Injection Concentrate. However, the products share the same indications of use, dosing, route of administration, frequency of administration, and method of preparation.

DMEPA met with the CMC review team on February 2, 2009 to discuss our label and labeling recommendations. We informed the CMC review team of our safety concerns if this Docetaxel Injection (b) (4) product was approved with the current labels and labeling. We noted that Taxotere has undergone extensive labels and labeling revisions to minimize the occurrence of medication errors. Because this product is prepared and administered in a manner similar to Taxotere, both DMEPA and the CMC review team concurred that both products should be labeled similarly. We discussed each of our label/labeling recommendations with the CMC review team and the team concurred. Additionally, DMEPA concurred with the following comments from the CMC review team, however, they will review the revised labels and labeling once they are resubmitted by the Applicant and may have additional comments forthcoming:

#### Container labels and carton labeling

1. On the container labels add the statements: “Sterile” and “Single Use Vial—Discard Unused Portion” for both injection concentrate as well as diluent.
2. Indicate where on the labels lot numbers and expiration would be printed.
3. Highlight the statement that the product should be stored protected from light.

#### Insert Labeling

“In section 3.2.P.5.1 of the original submission, for diluent specifications it is stated that volume of injection for 1.8mL is between (b) (4) and for 7.1mL fill is between (b) (4). However, the fill range shown in table 3 of the package insert states that for 1.8mL the range is 1.83-2.43mL while for 7.1mL the range is 7.3-7.9mL. Clarify the discrepancy between the body of the submission and package insert.”

### 1.3 PRODUCT INFORMATION

Docetaxel Injection (b) (4) is a microtubule inhibitor indicated for the treatment of breast cancer, non-small cell lung cancer, hormone refractory prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck. Docetaxel Injection (b) (4) has a boxed warning concerning certain precautions, contraindications, and adverse reactions. For dosage information, see Appendix A.

Docetaxel Injection is to be administered intravenously over 1 hour every 3 weeks. Contact of Docetaxel Injection (b) (4) with plasticized PVC (polyvinyl chloride) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the Docetaxel Injection diluted solution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Docetaxel Injection (b) (4) requires two dilutions prior to administration. Docetaxel infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Fully prepared Docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

Docetaxel will be available in single-dose vials containing 20 mg/0.5 mL and 80 mg/2 mL. The unopened vials can be stored at 20°C to 25°C (68°F to 77°F) and should be retained in the original package to protect from light. The product will be supplied in cartons containing 1 vial of active drug and 1 vial of diluent.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication errors prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

### 2.1 LABEL AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff to conduct a label, labeling, and/or packaging risk assessment (see Section 3, Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>2</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>3</sup>

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention and Analysis reviewed the following labels and labeling submitted by the Applicant on March 27, 2008. See Appendix B for pictures of the labels and labeling. Additionally, we referred to the corresponding container labels, carton and insert labeling for Taxotere obtained from the annual report dated July 10, 2008 (see Appendix C).

- Container Labels (active drug): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent container labels for the 20 mg and 80 mg active drug vials
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL
- Insert Labeling/Patient Package Insert (no image)

### **2.1.1 Docetaxel Injection (b) (4) and Taxotere Injection Concentrate Container Label and Carton Labeling Comparison**

We compared the container labels and carton labeling of the proposed Docetaxel Injection (b) (4) and Taxotere Injection Concentrate for the purpose of determining their similarities and differences.

The Taxotere Injection Concentrate container labels and carton labeling were obtained from the Annual Report for Taxotere Injection Concentrate submitted on July 10, 2008 which covers the period May 4, 2007 through May 13, 2008 (see Appendix C).

- Container Labels (active drug): 20 mg/0.5 mL and 80 mg/2 mL
- Diluent Container Labels for the 20 mg and 80 mg active drug vials
- Carton Labeling: 20 mg/0.5 mL and 80 mg/2 mL

## **3 RESULTS**

### **3.1 LABEL AND LABELING RISK ASSESSMENT**

#### **3.1.1 Proposed Labels and Labeling**

##### **3.1.1.1 General Comment for all Container Labels and Carton Labeling**

The (b) (4) is too prominent.

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<sup>3</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### 3.1.1.2 General Comments for Active Drug Container Labels and Carton Labeling

(b) (4) [80 mg/2 mL (40 mg/mL)] are not expressed in accordance with USP recommendations for the labeling of injectable drug products.

### 3.1.1.3 Carton Labeling

The caution statement contains words printed in bold black font (i.e., “Caution”, “entire”, “10 mg/mL”, and “10 mg/mL docetaxel after initial dilution”) that lack sufficient contrast.

### 3.1.1.4 Diluent Container Labels

The diluent labels contain the Docetaxel Injection statement of strength.

### 3.1.1.5 Insert Labeling

There is a typographical error in Section 2.9 “*Preparation and Administration*”, Step 2.

### 3.1.1.6 Patient Package Insert Labeling

DMEPA has no comments.

## 3.1.2 Docetaxel Injection (b) (4) and Taxotere Injection Concentrate Container Label and Carton Labeling Comparison

Review of the container labels and carton labeling identified areas of differences between Docetaxel Injection (b) (4) and Taxotere Injection Concentrate as stated below (also refer to Appendix D). Please note that in Tables 1 and 2, only the 20 mg strength container labels/carton labeling are shown since the 80 mg strength is similar. Table 3 reflects differences in the container label of the diluent and in the case where there are differences that need to be noted between the diluent for the 20 mg and 80 mg strengths, both labels are shown.

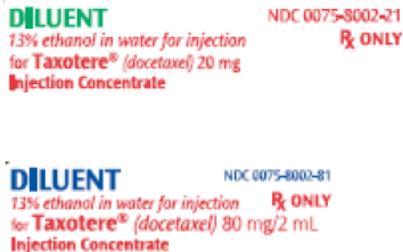
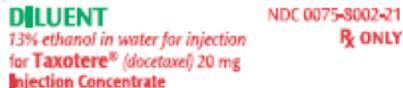
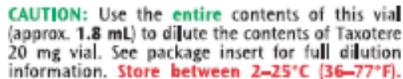
Table 1: Container Labels (Active Drug)		
Differences Identified	Docetaxel Injection (b) (4) (proposed)	Taxotere Injection Concentrate
The “Caution” statement on the proposed Docetaxel Injection labels does not give instructions for the two dilution step process whereas the Taxotere labels have this information.	(b) (4)	<b>CAUTION:</b> Withdraw the <b>entire</b> contents of diluent vial (approx. 1.8 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of <b>10 mg/mL</b> for the initial dilution. Use <b>only</b> the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information. <b>Store between 2–25°C</b>
The (b) (4) is on the proposed Docetaxel Injection labels whereas the Taxotere labels do not have this information.	(b) (4)	<b>20 mg/0.5 mL</b>

Table 1: Container Labels (Active Drug), cont'd

<p>The route of administration statement “For IV infusion only after final dilution” is on the side panel of Docetaxel Injection whereas Taxotere has this statement on the principal display panel.</p>	(b) (4)	
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Table 2: Carton Labeling

Differences Identified	Docetaxel Injection (proposed) (b) (4)	Taxotere Injection Concentrate
<p>The drug (b) (4) is on the labeling of the proposed Docetaxel Injection whereas the Taxotere labeling does not have this information.</p>	(b) (4)	<p><b>20 mg/0.5 mL</b></p>
<p>The caution statement on the side panel of Docetaxel Injection contains bolded words in black print (“Caution”, “entire”, “10 mg/mL”, and “10 mg/mL docetaxel after initial dilution”) whereas these words are in bold red print on the Taxotere carton.</p>		<p><b>CAUTION:</b> Withdraw the entire contents of 4 Lert vial (approximately 1.8 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of 10 mg/mL for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information. 10 mg/mL docetaxel after initial dilution.</p>
<p>The statement “Before Initial Dilution”, on the Docetaxel Injection 20 mg carton, immediately follows the strength whereas this statement is positioned below the strength on the corresponding Taxotere carton. Additionally, on the Docetaxel Injection carton, the statement is not followed by an asterisk with its accompanying notation placed beneath whereas on the Taxotere carton the statement is followed by an asterisk with the accompanying notation beneath.</p>		<p><b>20 mg/0.5 mL</b>  <b>Before Initial Dilution*</b>  *see back panel for initial concentration</p>

Table 3: Container Labels (Diluent)		
Differences Identified	Docetaxel Injection (b) (4) (proposed)	Taxotere Injection Concentrate
The proposed Docetaxel diluent labels have the Docetaxel drug (b) (4) statement on the label whereas the Taxotere diluent labels do not. (b) (4)	(b) (4)	
The diluent ingredients are listed on the side of the Docetaxel diluent labels whereas this information is located below the word “Diluent” on the Taxotere diluent labels.	(b) (4)	
The “Caution” statement on the proposed Docetaxel Injection diluent labels does not give instructions for use of the diluent whereas the Taxotere diluent labels have this information (i.e., “Caution: Use the entire contents...”)	(b) (4)	

#### 4 DISCUSSION

Our overall objective in comparing the proposed Docetaxel Injection (b) (4) container labels and carton labeling with the corresponding labels and labeling of Taxotere Injection Concentrate was to determine those important areas where the labels and labeling of Docetaxel Injection Concentrate do not correspond with those of Taxotere. The Taxotere labels/labeling have undergone several revisions since approval to highlight areas of confusion on the container and diluent labels and carton labeling that led to medication errors in the clinical setting.

Our analysis identified the following areas where the proposed Docetaxel Injection labels/labeling can be improved in order to make them safer to use and less vulnerable to confusion that could lead to medication errors.

## 4.1 CONTAINER LABELS AND CARTON LABELING

### 4.1.1 Prominence of the (b) (4)

The (b) (4) is prominent on the container labels, diluent labels, and carton labeling. The (b) (4) is larger than the print used for important information such as the strength and route of administration. Decreasing its size or deleting it would address this issue and provide additional room for other information.

### 4.1.2 Statement of Strength for Active Drug

(b) (4)

Thus, the (b) (4) should be deleted from the 20 mg/0.5 mL labels and labeling.

Additionally, the statement of strength [80 mg/2 mL (40 mg/mL)] is not presented in accordance with USP recommendations for the labeling of injectable drug products. According to the USP recommendations: *“For single dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses.”* Thus, the drug concentration (40 mg/mL) should be positioned immediately beneath the total drug content statement (80 mg/2 mL) and printed in a smaller size so that it has less prominence.

## 4.2 CONTAINER LABELS

### 4.2.1 Active Drug

The “Caution” statement on the Docetaxel Injection (b) (4) labels does not contain instructions for the two dilution step process or state the drug concentration obtained after the initial dilution step (it refers healthcare professionals to the insert labeling for instructions) whereas the Taxotere labels have this information (i.e., “Caution: Withdraw the entire contents of diluent...”). Since Docetaxel Injection (b) (4) requires two dilution steps prior to administration and this is not typical of an injectable product that is supplied in a liquid dosage form, we believe instructions for dilution that include the resultant concentration after the first dilution step should be presented on the container label so that healthcare practitioners are made immediately aware of the steps involved in preparing the product for administration. The Caution statement that is on the Docetaxel Injection (b) (4) carton labeling should be repeated on the container label. This information should be prominently displayed and boxed if possible. Our postmarketing experience with Taxotere showed that this information is essential to the safe use of the product. Without this information, practitioners were confused with how much drug was contained within each mL after the initial dilution step. Furthermore, should the carton or insert labeling become separated from the drug and diluent, the instructions for use will be readily available.

### 4.2.2 Diluent

The “Caution” statement on the Docetaxel Injection diluent labels does not give instructions for how to use the diluent (it refers healthcare professionals to the package insert for instructions) whereas the Taxotere diluent labels have the specific instructions (i.e., “Caution: Use the entire contents...”). Our postmarketing experience with Taxotere showed there was confusion about the two dilution step process and the amount of diluent required for diluting the active drug. Therefore, it is necessary to state on the label how the diluent is to be used and the actual amount to be used to dilute the active drug.

Furthermore, adding specific instructions for use of the diluent to the ‘Caution’ statement of the Docetaxel Injection Diluent will ensure that the information is readily available to healthcare providers should the diluent and active drug become separated from the insert labeling.

#### 4.2.3 Inappropriate Presentation of Strength on the Diluent Labels

The diluent labels contain the Docetaxel Injection (b) (4) statement (b) (4)

(b) (4) that draws attention to that section of the label. This is misleading and confusing and could lead to the diluent vial being confused as the active drug as seen with the Taxotere original labeling. Removing the (b) (4) from the diluent labels will help to minimize the potential for the diluent to be confused with the active drug.

#### 4.3 CARTON LABELING

Our postmarketing experience with Taxotere showed that when the entire “Caution” section was printed in red with the words “Caution”, “entire”, and “10 mg/mL” printed in bold red font, we received medication error reports with complaints that the concentration obtained after the initial dilution step was not prominent on the labeling (i.e., 10 mg/mL). The current Taxotere presentation of the Caution statement (it has “Caution”, “entire”, “10 mg/mL”, and “10 mg/mL docetaxel after initial dilution” in bold red font and all other wording in black print) is a result of DMEPA’s recommendations for means to help resolve the issue.

The Caution statement on the side panel of the proposed carton labeling contains words printed in bold black font (i.e., “Caution”, “entire”, “10 mg/mL”, and “10 mg/mL docetaxel after initial dilution”). Putting this information in bold black font does not provide sufficient contrast with the surrounding black text as was the case with the all red statement of Taxotere. Highlighting only the bolded words using a different color (e.g., red, like Taxotere) will help to emphasize these words even more and draw healthcare practitioners’ attention to this information.

The statement of strength on the proposed 20 mg carton is immediately followed by the statement “Before Initial Dilution”. This statement should be positioned below the strength so that it does not interfere with its prominence. On the Taxotere carton, “Before Initial Dilution” is followed by an asterisk and the referenced statement “\*see back panel for initial concentration” is placed below. This recommendation was made by DMEPA to help guide healthcare practitioners to the caution statement on the back panel which states the 10 mg/ml concentration that results after the initial dilution step.

#### 4.4 INSERT LABELING

We noted a typographical error in Section 2.9 “*Preparation and Administration*”, Step 2. See Section 6 of this review for our recommendation for clarification of the wording.

### 5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks we have identified can be addressed and mitigated prior to drug approval and provide recommendations in Section 6 that aim at reducing the risk of medication errors.

## 6 RECOMMENDATIONS

### 6.1 COMMENTS TO THE DIVISION

DMEPA met with the CMC review team on February 2, 2009 to discuss our label and labeling recommendations. We informed the CMC review team of our safety concerns if this Docetaxel Injection (b)(4) product was approved with the current labels and labeling. We noted that Taxotere has undergone extensive labels and labeling revisions to minimize the occurrence of medication errors. Because this product is prepared and administered in a manner similar to Taxotere, both DMEPA and the CMC review team concurred that both products should be labeled similarly. We discussed each of our label/labeling recommendations with the CMC review team and the team concurred. Additionally, DMEPA concurred with the following comments from the CMC review team, however, they will review the revised labels and labeling once they are resubmitted by the Applicant and may have additional comments forthcoming:

#### Container labels and carton labeling

1. *On the container labels add the statements: “Sterile” and “Single Use Vial—Discard Unused Portion” for both injection concentrate as well as diluent.*
2. *Indicate where on the labels lot numbers and expiration would be printed.*
3. *Highlight the statement that the product should be stored protected from light.*

#### Insert Labeling

*“In section 3.2.P.5.1 of the original submission, for diluent specifications it is stated that volume of injection for 1.8mL is between (b)(4) and for 7.1mL fill is between (b)(4). However, the fill range shown in table 3 of the package insert states that for 1.8mL the range is 1.83-2.43mL while for 7.1mL the range is 7.3-7.9mL. Clarify the discrepancy between the body of the submission and package insert.”*

Please incorporate the comments from the CMC review team in the label and labeling recommendations sent to the Applicant.

We would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

### 6.2 COMMENTS TO THE APPLICANT

The labels and labeling of Taxotere Injection Concentrate (the RLD) have undergone several revisions over the years in order to address medication error reports concerning drug preparation errors. These errors were due to confusing presentation of the active drug concentration and volume, diluent volume, and instructions for preparation. We believe the current Taxotere labels/labeling are better designed as a result of the revisions they have undergone. Having the proposed Docetaxel Injection (b)(4) reflect those changes in specific areas will also make for better designed labels/labeling of Docetaxel Injection as well. Therefore, we have the following recommendations.

#### **A. General Comment for the all Container Labels and the Carton Labeling**

The (b)(4) is too prominent on the labels. Decrease the prominence (b)(4) by decreasing its size. Alternatively, delete (b)(4).

## B. Container Labels

### 1. Active Drug

- a. The “Caution” statement does not contain instructions for the two dilution step process or state the drug concentration obtained after the initial dilution step. Delete the current caution statement wording (i.e., “See package insert...”) and provide instructions for the two dilution step process and state the drug concentration obtained after the initial dilution step (i.e., use the same caution statement that is on the carton labeling). Replace the bolded text with a contrasting colored bold font. Additionally, box the caution statement if possible, and/or increase the font size of “10 mg/mL”.
- b. (b) (4)  
(b) (4) Therefore, delete the (b) (4)  
(b) (4) from the 20 mg/0.5 mL labels and labeling.
- c. The statement of strength [80 mg/2 mL (40 mg/mL)] is not presented in accordance with USP recommendations for the labeling of injectable drug products. According to the USP recommendations: *“For single dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses.”* The following is the recommended presentation: position the drug concentration (40 mg/mL) immediately beneath the total drug content statement (80 mg/2 mL) and decrease its size so that it has less prominence (see example below).

80 mg/2 mL (40 mg/mL)
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### 2. Diluent

- a. The diluent labels contain the Docetaxel Injection (b) (4) statement (b) (4)  
(b) (4) that draws attention to that section of the label. This is confusing and may cause the diluent to be mistaken as the active drug. Delete the Docetaxel Injection (b) (4)  
(b) (4) Revise the statement to “Diluent for Docetaxel Injection (b) (4) 20 mg” (state the appropriate strength accordingly), or similar verbiage, to identify the diluent. Continue to ensure that the word “Diluent” is the most prominent word on the label.
- b. The “Caution” statement on the Docetaxel Injection diluent labels does not give instructions for how to use the diluent. Delete the current caution statement wording (b) (4)  
(b) (4) and provide specific instructions for use of the diluent on the principal display panel, specifically highlighting the quantity to be used for dilution.

## C. Carton Labeling

1. See Comments B-1-b and B-1-c, above, that concern the statements of strength.
2. The Caution statement on the side panel contains words printed in bold black font (i.e., “Caution”, “entire”, “10 mg/mL”, and “10 mg/mL docetaxel after initial dilution”) that lack sufficient contrast with the surrounding text. Highlight these bolded words using a different color

(e.g., red, like Taxotere) in order to provide more prominence and emphasis. Additionally, box the caution statement and/or increase the font size of “10 mg/mL”.

3. Position the statement “Before Initial Dilution” below the statement of strength. Additionally, place an asterisk next to the statement and place the accompanying notation (that directs practitioners to the caution statement for information on the concentration that results after the initial dilution step) immediately below it. See the following example:

STATEMENT OF STRENGTH Before Initial Dilution* *see side panel for concentration obtained after initial dilution step
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#### **D. Insert Labeling**

There is a typographical error noted in Section 2.9 “Preparation and Administration”, Step 2. The text states “Aseptically withdraw ... (approximately 1.8 mL **or** docetaxel injection...)”. Please change the word “or” to “for”.

## APPENDICES

## Appendix A: Docetaxel Injection (b) (4) Indications and Dosage

Indication	Dosage
Breast cancer: locally advanced or metastatic	60 mg to 100 mg/m <sup>2</sup> single agent
Breast cancer adjuvant	75 mg/m <sup>2</sup> administered 1 hour after doxorubicin 50 mg/m <sup>2</sup> and cyclophosphamide 500 mg/m <sup>2</sup> every 3 weeks for 6 cycles
Non-small cell lung cancer, after platinum therapy failure	75 mg/m <sup>2</sup> single agent
Non-small cell lung cancer, chemotherapy naïve	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup>
Hormone refractory prostate cancer	75 mg/m <sup>2</sup> with 5 mg prednisone twice a day continuously
Gastric adenocarcinoma	75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup> (both on day 1 only) followed by fluorouracil 750 mg/m <sup>2</sup> per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion
Squamous cell carcinoma of the head and neck	<u>Induction chemotherapy followed by radiotherapy:</u> 75 mg/m <sup>2</sup> followed by cisplatin 75 mg/m <sup>2</sup> IV (day 1), followed by fluorouracil 750 mg/m <sup>2</sup> per day as a 24-hour IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles <u>Induction chemotherapy followed by chemoradiotherapy:</u> 75 mg/m <sup>2</sup> followed by cisplatin 100 mg/m <sup>2</sup> IV (day 1), followed by fluorouracil 1000 mg/m <sup>2</sup> per day as a 24-hour IV (days 1-4); for 3 cycles
<b>Premedication Regimen</b>	Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration.  Hormone refractory prostate cancer: oral dexamethasone 8 mg, at 12, 3, and 1 hours before treatment

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