CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022312 SUPPL # HFD # 150

Trade Name N/A

Generic Name Docetaxel Injection

Applicant Name Apotex, Inc.

Approval Date, If Known January 11, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Product is pharmaceutically equivalent to the RLD. Only has a different qualitative and quantitative formulation. Applicant was granted a waiver for bioequivalence.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020449 (RLD) Taxotere (docetaxel) Injection

NDA# 201195, 201525, 22234, and 22534 (other (b)(2) apps) Docetaxel Injection

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Christy Cottrell
Title: Regulatory Project Manager
Date: January 11, 2012

Name of Office/Division Director signing form: Anthony J. Murgo, MD
Title: Associate Director, OHOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

CHRISTY L COTTRELL
01/11/2012

ANTHONY J MURGO
01/11/2012

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

EXCLUSIVITY STATEMENT

According to the information published in the *Approved Drug Products with Therapeutic Equivalence Evaluations* list, 28th Edition, sanofi-aventis, U.S. LLC is entitled to the following marketing exclusivity for Taxotere® (Docetaxel) for Injection 40 mg (base)/mL under the following exclusivity codes:

Exclusivity Code	Exclusivity Expiration
I-436 (FOR USE IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE FOR THE ADJUVANT TREATMENT OF PATIENTS WITH OPERABLE NODE-POSITIVE BREAST CANCER)	August 18, 2007
I-490 (FOR USE IN COMBINATION WITH CISPLATIN AND FLUOROURACIL FOR THE TREATMENT OF PATIENTS WITH ADVANCED GASTRIC ADENOCARCINOMA, INCLUDING ADENOCARCINOMA OF GASTROESOPHAGEAL JUNCTION, WHO HAVE NOT RECEIVED PRIOR CHEMOTHERAPY FOR ADVANCED DISEASE)	March 22, 2009
I-519 (USE OF TAXOTERE (DOCETAXEL) INJECTION CONCENTRATE IN COMBINATION WITH CISPLATIN AND FLUOROURACIL FOR THE INDUCTION OF PATIENTS WITH INOPERABLE LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN))	October 17, 2009
I-542 (EXPANSION OF PATIENT POPULATION FOR HEAD AND NECK CANCER FROM "INOPERABLE" PATIENTS TO ALL PATIENTS)	September 28, 2010
I-543 (USE IN COMBINATION WITH CISPLATIN AND FLUOROURACIL FOR THE INDUCTION TREATMENT OF PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN))	September 28, 2010

Apotex Inc. certifies that the sale of Docetaxel Injection 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL) will not begin until after the expiry of the exclusivity for I-542 and I-543.

Date: March 27, 2008

Bernice Tao
Director, Regulatory Affairs US

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3849 • www.apotex.com

MEMBER CGPA

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-312 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DDOP PDUFA Goal Date: 1-28-09 Stamp Date: 3/28/2008

Proprietary Name: Docetaxel Injection

Established/Generic Name: docetaxel injection

Dosage Form: Injection

Applicant/Sponsor: Apotex, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):5
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Breast Cancer: Single agent for locally advanced or metastatic breast cancer 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.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

Christy Cottrell
12/2/2008 02:38:57 PM
This is a 505(b)(2) application- no new active ingredient, no new indication, population, dosage form, etc. PREA not triggered.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022312 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Docetaxel Injection (b) (4) Dosage Form: Injection		Applicant: Apotex, Inc. Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: DOP1/HFD-150

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 020449 Taxotere

Provide a brief explanation of how this product is different from the listed drug.

Different qualitative and quantitative formulation

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 1-11-12

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 12, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response letters issued on 5/4/11, 9/22/10, 1/29/10, 4/28/09

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☒ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☒ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 1/11/12 Complete Response: 5/4/11, 9/22/10, 1/29/10, 4/28/09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	Included

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Included
• Original applicant-proposed labeling	Included
• Example of class labeling, if applicable	Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 12/21/11, 4/6/11, 1/26/10, 2/27/09 ☐ DRISK ☒ DDMAC 4/15/09 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	4/21/09
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 12/5/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 1/11/12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: 505(b)(2) - PERC not needed • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/15/11, 4/29/11, 9/22/10, 1/29/10, 4/28/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1/10/12, 4/27/11
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	12/19/11, 3/10/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See MOR
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/12/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/11/09, 4/22/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 9/22/10, 1/28/10, 4/28/09
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 4/28/09, 5/21/08
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/2/11, 4/21/11, 9/22/10, 1/22/10, 4/23/09
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 12/1/11, 9/17/10, 9/1/10, 1/12/10, 4/23/09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 4/26/11

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 8/22/11 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

From: Duvall Miller, Beth A
Sent: Wednesday, April 27, 2011 5:12 PM
To: Cottrell, Christy L.
Cc: Kim, Tamy; Kacuba, Alice; Cross Jr, Frank H
Subject: NDA 22-312, docetaxel for injection - cleared for action (again)

Attachments: N22312_assessment form.doc

Christy,

We discussed your application at Monday's clearance meeting and you are cleared again for action from a 505(b)(2) perspective. My understanding is that this application is heading for CR again; if some reason you are now planning on approval, please let me know as there was one loose end that we didn't reach a final decision on that I would need to 'clear'. (b) (4)

Finally, please make the following revisions to your 505(b)(2) assessment before archiving in DARRTS, but also defer finalizing in DARRTS until you are heading towards approval. I've attached the version you previously sent in 2009 (I think that's the one and only version we got, which is fine) and made some mark-ups within as indicated below in the list.

- Under Application Information please update the PDUFA Goal Date and make sure the indications listed are the ones Apotex still seeks (i.e., if Apotex is now seeking the H/N indications)
- Q4: please see marked-up edits and comments within attached doc. Please make sure that the appropriate reason for granting the waiver for *in vivo* bioequivalence data is correctly captured in assessment and documented in appropriate reviews (see also further below in this email string where this issue was raised).
- Q11: Please confirm that these products are pharmaceutical equivalents as opposed to pharmaceutical alternatives and update responses to Q11 and Q12 accordingly. Then update and potentially move the list of other PE/PA products by omitting Taxotere from the list since it's the product relied-upon in the application and the Hospira product NDA 22234 is now approved. (see mark-ups and comments in attached)
- Q15: Under the Para IV information where you indicated the applicant had been sued for patent infringement, please indicate that the 30-month stay of approval expired 12/30/10.

Finally, I note that the attached assessment is an older version of the assessment, but there's no need for you to complete a new one. Just make the changes to this version as indicated above and archive in DARRTS as you head towards approval.

N22312_assess
ent form.doc (17

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Quaintance, Kim M
Sent: Wednesday, May 12, 2010 2:43 PM
To: Kacuba, Alice
Cc: Kim, Tamy; Duvall Miller, Beth A; Tilley, Amy
Subject: RE: NDA 22-312, docetaxel for injection - cleared for action

Hi Alice,

We discussed this application at yesterday's clearance meeting, and it is cleared for action from a (b)(2) perspective. If you can resolve the CMC issues and plan to take a TA action this time, please send the letter through us (Beth and I) for a quick (we promise!) look. The TA letter template has been updated so make sure you pull the new template from the CST eRoom.

We are now advising RPMs not to finalize the (b)(2) assessment until the application is approved, so if you haven't yet done so, please hold off for now. However, do not fret if it has already been entered into DARRTS; an addendum can always be prepared if necessary.

Please let me know if you have any questions.
Kim

From: Kacuba, Alice
Sent: Thursday, May 06, 2010 2:54 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?
Importance: High

May be CMC deficiencies again (b) (4)

However, CMC says they are using the same manuf facilities for this application so they think that it may affect this application too. What fun! Always something, isn't there.

From: Duvall Miller, Beth A
Sent: Thursday, May 06, 2010 2:47 PM
To: Kacuba, Alice
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

That's what I thought, thanks for confirming.

Do you think it will be a TA or are there deficiencies (again) that will make it a CR?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
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Fax: (301) 796-9855

From: Kacuba, Alice
Sent: Thursday, May 06, 2010 2:28 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

Beth,

The suit has not been resolved yet, so best they could get is a TA again.

Thanks.
Alice

From: Duvall Miller, Beth A
Sent: Thursday, May 06, 2010 1:47 PM
To: Kacuba, Alice
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

Hi Alice,

Did you have a chance to find out the status of the patent infringement suit?

I'd like to send the b(2) agenda out by COB today, but definitely must get it out by tomorrow. Any updates would be appreciated.

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Kacuba, Alice
Sent: Monday, May 03, 2010 9:10 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

I am out Tuesday and will be back in office Wed and will give you an update. Is that too late?

From: Duvall Miller, Beth A
Sent: Monday, May 03, 2010 3:22 PM
To: Kacuba, Alice
Cc: Quaintance, Kim M; Kim, Tamy
Subject: FW: NDA 22-312, docetaxel for injection - planned action this cycle?

Hi Alice,

Sorry to bother you. I just got Amy's out of office message; looks like she won't be back until Monday, the date of our clearance meeting. Do you know the status of this application, specifically the patent infringement law suit?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
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OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Duvall Miller, Beth A
Sent: Monday, May 03, 2010 3:20 PM
To: Tilley, Amy
Cc: Quaintance, Kim M; Kim, Tamy; Cottrell, Christy L.
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

Hi Amy,

I'm preparing the updated summary of this application (the resubmission) for Monday's 5/10 clearance meeting.

Can you please update me on the status of the patent infringement suit that filed was against Apotex re: Taxotere patents 5438072, 5698582, 5714512, and 5750561 – has it been resolved been resolved? I checked the resubmission in the EDR, but it looks like it primarily addresses the CMC/micro deficiencies and updated labeling. The updated labeling does carve out the H/N cancer indications, but I did not see any reference in the resubmission regarding the infringement lawsuit.

Please reply to all in your response.

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Cottrell, Christy L.
Sent: Thursday, April 29, 2010 3:29 PM
To: Duvall Miller, Beth A; Tilley, Amy
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

Beth,

Amy Tilley is handling this application for me. Amy- can you respond to Beth's inquiry?

Thanks,
Christy

From: Duvall Miller, Beth A
Sent: Thursday, April 29, 2010 3:15 PM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - planned action this cycle?

Hi Christy,

We'll be discussing your application (RS) at the upcoming clearance meeting on May 10th – are you planning to approve this application this cycle, i.e., have the patents expired or otherwise been resolved? I have your PDUFA due date as 5/24, is that correct?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
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Fax: (301) 796-9855

From: Cottrell, Christy L.
Sent: Friday, January 08, 2010 10:22 AM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Kim, Tamy
Subject: RE: NDA 22-312, docetaxel for injection - b2 clearance

Beth,

This will end up being a Complete Response (again)- CMC/Micro issues. The PDUFA date is 1/29. I don't think we'll be taking action much earlier than that.

Christy

From: Duvall Miller, Beth A
Sent: Wednesday, January 06, 2010 11:01 AM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Kim, Tamy
Subject: NDA 22-312, docetaxel for injection - b2 clearance

Hi Christy,

Just checking in with you on this application. I realize the RS arrived back in July and the due date for this application is 1/30/2010. What action are you planning this cycle and when?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Duvall Miller, Beth A
Sent: Monday, March 30, 2009 4:37 PM
To: Duvall Miller, Beth A; Cottrell, Christy L.
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - recommendations for TA action

I meant to also say if you are planning on a TA action after all, please send us your draft letter so we can help craft the language I referred to below.

Beth

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Duvall Miller, Beth A
Sent: Monday, March 30, 2009 4:36 PM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: NDA 22-312, docetaxel for injection - recommendations for TA action

Hi Christy,

We discussed your application again at today's clearance meeting. With OCC's input, we advise the following with respect to taking a TA action:

- For the purposes of the labeling, please revise the label to once again include all 5 of the indications that Apotex sought in the original application including the H/N and gastric cancer indications that had been carved out because of unexpired patents/exclusivity. We recognize this is a different approach from the one taken in the Hospira docetaxel b(2) application but we believe this is the cleanest approach for administratively acting on this application.
- For the TA letter, we will help you craft language that alludes to the existing patents and exclusivities without implying the date that the patents expire (as the Hospira TA letter) did

since those patent protections and exclusivities are numerous and complex.

However, if you are still planning a CR as indicated below, these instructions are a moot point. But please file this away for future reference when it's time to issue a TA letter. As always, we will need to clear your application before each and every action.

Let me know if you have any questions. Glen attended today's meeting too so he may be able to help shed some light on this advice.

Beth

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
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Fax: (301) 796-9858

From: Cottrell, Christy L.
Sent: Tuesday, March 17, 2009 3:39 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

I'll know more next week. If it's going to be a CR, we may do it sooner. I'll let you know.

Christy

From: Duvall Miller, Beth A
Sent: Tuesday, March 17, 2009 3:38 PM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

Thanks for the heads up – we will still need to clear the application for any kind of action. And if there are b(2)-related deficiencies, we would definitely want those included in your CR letter.

We have your action date as 4/28/09 – please let us know if you are planning on taking an action sooner than that.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Cottrell, Christy L.
Sent: Tuesday, March 17, 2009 3:30 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

Beth,

Just so you're up-to-date….it is possible that this application is headed for a Complete Response action. I should have a final decision on that next Thursday, 3/26. There were several outstanding CMC/Micro Information Requests to which the applicant just responded late last week. We don't know yet whether the responses are adequate or not. Team meeting next week to discuss.

Christy

From: Duvall Miller, Beth A
Sent: Tuesday, March 17, 2009 3:21 PM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

Thanks Christy. We'll discuss this response with OCC/ORP at our next clearance meeting (3/30) and get back to you.

Beth

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9858

From: Cottrell, Christy L.
Sent: Tuesday, March 17, 2009 2:27 PM
To: Duvall Miller, Beth A
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

See attached feedback from ONDQA team re: Bioequivalence waiver.

<< Message: RE: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions >>
Christy

From: Duvall Miller, Beth A
Sent: Tuesday, March 17, 2009 10:46 AM
To: Cottrell, Christy L.
Cc: Quaintance, Kim M; Jones, Glen D (CDER)
Subject: NDA 22-312, docetaxel for injection - f/up b(2) clearance questions

Hi Christy,

We discussed your application with ORP/OCC at yesterday's b(2) clearance meeting and do have some f/up questions for you regarding the waiver of bioequivalence studies.

According to your b(2) assessment, "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."

21 CFR 320.22 (b)1 gives the following criteria for granting such a waiver (key points highlighted in yellow):

b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Your assessment goes on to say that "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 fact that the b(2) docetaxel has a different excipient than Taxotere appears to contradict the criteria spelled out in 21 CFR 320.22 (b)1 above which leaves us wondering whether or not there is some other reason the waiver was granted. It appears that a similar waiver was requested and granted to Hospira for their docetaxel application (TA on 8/11/08).

The text quoted from your b(2) assessment appears to be taken from the clin pharm review I found in DFS (attached). That review also indicates an ONDQA decision on this but I could not find such a review or memo in both DFS or in DARRTS (under IND 78,376) although I did find a short OCP memo from 9/2007 in DARRTS (also attached). Is there some other documentation that explains why the BE waiver was granted? I'm also attaching the CMC review for this application which does not mention the BE waiver.

We may also have some f/up questions regarding the carving out of indications in the label, but we'll save that for a separate email as we're still doing some homework on that one.

Beth

<< File: N22312 BE waiver review.pdf >> << File: N22312 CMC review.pdf >> << File: N22312 OCP review.pdf >>

Beth Duvall-Miller
Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY L COTTRELL
01/12/2012

From: Cottrell, Christy L.
Sent: Tuesday, November 22, 2011 2:55 PM
To: 'kkrishna1@apotex.com'
Subject: NDA 022312 for Docetaxel Injection: Request for labeling revision

Importance: High

Kiran,

Please refer to your pending NDA 022312 for Docetaxel Injection. See below for a request from the CMC reviewer for a change to the carton/container labeling.

- Revise your proposed carton and container labels for Docetaxel Injection (Concentrate) and Docetaxel Injection (Diluent) to include the Lot No. and Expiration date printed in the mock up labels.

Please submit your revised labeling by Wednesday, November 30, 2011. Feel free to contact me with any questions.

Regards,
Christy Cottrell

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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/s/

CHRISTY L COTTRELL
11/22/2011

From: Cottrell, Christy L.
Sent: Monday, October 03, 2011 10:54 AM
To: 'kkrishna1@apotex.com'
Subject: NDA 022312 for Docetaxel Injection: Labeling information request

Importance: High

Kiran,

Please refer to your pending NDA 022312 for Docetaxel Injection. Below are comments from OSE regarding the carton/container labeling.

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) We recommend you (b) (4) in order to improve the visibility of the established name.

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

- Box the caution statement.

Diluent Labeling

- Place the following in the caution statement in bold font: **"1.8 mL"** and **"7.1 mL"**.

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

- 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.

- Revise the statement (b) (4) to read "Single Use Vials".

Please implement these revisions and submit revised carton/container labeling by October 17, 2011. Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
10/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Apotex Inc.
Attention: Michael Balon
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Dear Mr. Balon:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Alice Kacuba, Chief Project Manager Staff, at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

ALICE KACUBA
09/29/2011
Signing for Dr. Justice.

MEMORANDUM OF TELECONFERENCE MINUTES

TELECON DATE: August 4, 2011
TIME: 12:00pm
APPLICATION: NDA 022312
DRUG NAME: Docetaxel Injection
TYPE OF MEETING: Informal regulatory guidance telecon

FDA ATTENDEES: Christy Cottrell, DDOP

EXTERNAL CONSTITUENT ATTENDEES: Kiran Krishnan, Apotex, Inc.

BACKGROUND:
On May 4, 2011, FDA issued a Complete Response letter for NDA 022312 for Docetaxel Injection. That letter was the fourth Complete Response letter issued for the application. On July 12, 2011, the applicant provided a resubmission addressing deficiencies from the Complete Response letter. In a team meeting on July 28, 2011, it was determined that this would be designated as a Class 2 resubmission with a 6 month PDUFA goal date. On August 3, 2011, the applicant inquired about the classification and PDUFA due date. I notified them of the Class 2 designation and PDUFA date of January 12, 2012. The applicant then requested an appeal and explained that they believe this submission qualifies as a Class 1 resubmission. On August 4, 2011, at 12:00pm, I spoke with Mr. Krishnan from Apotex, Inc. to explain the rationale for classifying this as a Class 2 resubmission. Details of that discussion are outlined below.

DISCUSSION:
I began by explaining to Mr. Krishnan that following his email appeal request of August 3, 2011, numerous staff had discussed this application and his concerns about the Class 2 designation. I gave him the names of those involved in the discussions: Alice Kacuba (Chief Project Management Staff), the CMC review team, Sarah Pope (Branch Chief-ONDQA) and Rik Lostritto (Division Director-ONDQA). I went on to state that the primary reason this was designated as a Class 2 resubmission was because there was a cGRMP compliance deficiency in the last action letter, therefore, any resubmission automatically requires an EES request, triggering the Class 2 designation. I stated that this was a regulatory requirement and was not negotiable. Mr. Krishnan argued that Apotex has received an Acceptable inspection and had included the letter with the submission. I explained that we cannot just "take Apotex's word for it" and that there are internal processes for requesting inspection updates from the District Offices. I further explained that a formal request must be sent to the District Office, then they make a determination about whether an inspection is required, they forward a report to us at headquarters and then we must review the report.

In addition, I reminded Mr. Krishnan of the outstanding gratuitous amendments from the last review cycle that were still outstanding and required review. He asked why they were not reviewed in the last cycle. I explained that at the time of their submission, we already knew that there were "fatal" compliance issues that would result in a Complete Response action and that it

was decided that we would not expend any additional resources on this application when we knew there would not be a positive action. I reminded Mr. Krishnan that in the cover letter for the current resubmission, Apotex asked that the gratuitous amendments be reviewed in this cycle. I also informed him that the amendments contained a large amount of new data requiring in-depth CMC review and microbiology consultation. He once again replied that the amendments should have been reviewed in the last cycle and that he did not believe they should impact the Class 1/2 designation for this cycle. I reminded him that even if the amendments had been reviewed last cycle, this resubmission would still have been a Class 2 based on the outstanding compliance issues.

At this point in the discussion, Mr. Krishnan acknowledged the rationale for the designation but noted that it is different than the way Office of Generics operates. I informed him that the processes for each Office are different and that the company should familiarize themselves with the policies of the Office of New Drugs, given that this is Apotex's first NDA.

Mr. Krishnan asked that the Division honor Apotex's request for an expedited review of this resubmission. I informed him that with a Class 2 designation, we have 6 months to review the submission and that I could not guarantee an expedited review. He acknowledged my statement, but again reiterated that they would appreciate a quick review. I told him that I would pass the request along to the review team, but noted that they are working on multiple applications simultaneously, and that it is unlikely that this application would receive an expedited review. I told Mr. Krishnan that if he still had concerns about the Class 2 designation and associated review timeline, that he should follow the procedure for formal dispute resolution and send a letter to Dr. Rick Pazdur.

_____

Christy Cottrell
Regulatory Project Manager

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/s/

CHRISTY L COTTRELL
09/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312 **INFORMATION REQUEST**

Apotex Corp.
US Agent for Apotex Inc.
Attention: Kiran Krishnan
Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Mr. Krishnan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL.

We also refer to your July 12, 2011, submission in response to the FDA Complete Response letter dated May 4, 2011, and to your January 27, 2011, amendment. We have the following comment and requests for additional information. Please submit your written response no later than Friday, August 12, 2011.

> Clarify if the manufacturing and sterilization equipment used at the Apotex Richmond Hill site for the docetaxel diluent is the same as that used at the Apotex Signet Campus for the docetaxel concentrate.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
08/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM: Division of Drug Oncology Products	
Mail: OSE			Christy Cottrell, RPM	
DATE August 8, 2011	IND NO.	NDA NO. NDA 022312	TYPE OF DOCUMENT New NDA (Class 2 resubmission)	DATE OF DOCUMENT July 12, 2011
NAME OF DRUG Docetaxel Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE October 30, 2011

NAME OF FIRM: Apotex, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- X RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a Class 2 Resubmission (review cycle #5) for a new 505(b)(2) NDA for Docetaxel Injection. Request that DMEPA and DRISK review product labeling and PPI and provide comments by October 30, 2011. PDUFA date is January 12, 2012, with a target action date sometime in December. Link to submission is: \\CDSESUB1\EVSPROD\NDA022312\022312.enx. Assigned reviewers will be invited to labeling meetings.

CMC Reviewer = Josephine Jee
PM = Christy Cottrell

SIGNATURE OF REQUESTER Christy Cottrell	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

CHRISTY L COTTRELL
08/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312

ACKNOWLEDGE – CLASS 2 RESPONSE

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Attention: Kiran Krishnan
Director, Regulatory Affairs

Dear Mr. Krishnan:

We acknowledge receipt on July 12, 2011, of your July 12, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection 40 mg/mL (20 mg/0.5mL and 80 mg/2mL).

We consider this a complete, class 2 response to our May 4, 2011, action letter. Therefore, the user fee goal date is January 12, 2012.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
08/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**
Jim McVey/ Vera Viehmann

E-mail to: **CDER OPS IO MICRO**
Paper mail to: **WO Bldg 51, Room 4193**

FROM: Deborah Mesmer, ONDQA PM, 301.796.4023

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
08/03/11		022312	Amendment NDA Resubmission	January 27, 2011 July 12, 2011

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
Docetaxel injection	Class 2 resubmission	January 12, 2012	October 10, 2011

NAME OF APPLICANT OR SPONSOR:
Apotex

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS: This is the fifth review cycle for this NDA.

Requesting microbiology review for the amendment dated January 27, 2011, which was submitted but not reviewed in the 4th review cycle. This amendment provides changes/corrections of equipment, manufacturing/packaging process (b) (4) NDA was resubmitted July 12, 2011

The submission is electronic.

Chemistry reviewer: Josephine Jee
Project Manager for Quality: Debbie Mesmer
DDOP Project Manager: Christy Cottrell

Please advise Debbie Mesmer of assigned reviewer.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

■ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

■EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

DEBORAH M MESMER
08/03/2011

From: Mesmer, Deborah
Sent: Thursday, March 10, 2011 1:15 PM
To: McVey, James; CDER OPS IO MICRO; Gantt, Sylvia
Cc: Mesmer, Deborah; Jee, Josephine M; Hussong, David; Cottrell, Christy L.; Pope Miksinski, Sarah
Subject: Please cancel this request- - FW: Finalized - NDA 22312 CMC Micro & Sterility Assurance Review Request (FRM-CONSULT-25)

Hello,

Please **cancel** this microbiology consult request dated March 8, 2011 for NDA 22312 for the amendment dated January 27, 2011.

Thank you.

Debbie

Deborah Mesmer
Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023; p
deborah.mesmer@fda.hhs.gov

From: Mesmer, Deborah
Sent: Tuesday, March 08, 2011 6:28 PM
To: McVey, James; CDER OPS IO MICRO
Subject: FW: Finalized - NDA 22312 CMC Micro & Sterility Assurance Review Request (FRM-CONSULT-25)

Requesting consult for pending NDA in DDOP. Requested completion date is April 7, 2011.

Thank you.

Debbie

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Tuesday, March 08, 2011 6:26 PM
To: Gantt, Sylvia; Mesmer, Deborah; Jee, Josephine M; Hussong, David; McVey, James; Cottrell, Christy L.
Subject: Finalized - NDA 22312 CMC Micro & Sterility Assurance Review Request (FRM-CONSULT-25)

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/s/

DEBORAH M MESMER
03/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**
David Hussong/Jim McVey/Sylvia Gantt

E-mail to: **CDER OPS IO MICRO**
Paper mail to: **WO Bldg 51, Room 4193**

FROM: Deborah Mesmer, ONDQA PM, 301.796.4023

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
03/08/11		022312	amendment	January 27, 2011

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
Docetaxel injection		May 17, 2011	April 7, 2011

NAME OF APPLICANT OR SPONSOR:
Apotex

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

Requesting microbiology review for the amendment dated January 27, 2011. This amendment provides changes/corrections of equipment, manufacturing/packaging process (b) (4)

The submission is electronic.

Chemistry reviewer: Josephine Jee
Project Manager for Quality: Debbie Mesmer
DDOP Project Manager: Christy Cottrell

Please advise Debbie Mesmer of assigned reviewer.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):
■ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):
■EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

DEBORAH M MESMER
03/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312

ACKNOWLEDGE – CLASS 2 RESPONSE

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Attention: Kiran Krishnan
Director, Regulatory Affairs

Dear Mr. Krishnan:

We acknowledge receipt on November 15, 2010, of your November 12, 2010, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL.

We consider this a complete, class 2 response to our September 22, 2010, action letter. Therefore, the user fee goal date is May 15, 2011.

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

CHRISTY L COTTRELL
02/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Division of Drug Oncology Products Christy Cottrell, RPM	
DATE January 12, 2011	IND NO.	NDA NO. NDA 022312	TYPE OF DOCUMENT Class 2 Resubmission	DATE OF DOCUMENT November 15, 2010
NAME OF DRUG Docetaxel Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 15, 2011

NAME OF FIRM: Apotex, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a Class 2 resubmission in response to a Complete Response letter (4th review cycle). There are outstanding issues with the carton and container labeling, therefore, DDOP is requesting DMEPA review of the labels and attendance at labeling meetings (TBS). Prior DMEPA reviewers were: Loretta Holmes and Kristine Arnwine. PDUFA date is May 15, 2011. Requesting completed review one month prior = April 15, 2011. Links to the submission is below:

EDR Location: \\CDSESUB1\EVSPROD\NDA022312\0026
Gateway Location: \\fdswa132\cderesub\inbound\ectd\ci1289599190024.213930@llnap13 te

CMC reviewer = Josephine Jee
PM = Christy Cottrell

SIGNATURE OF REQUESTER Christy Cottrell	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

CHRISTY L COTTRELL
01/12/2011

Memorandum

To: NDA 22-312
cc: Haripada Sarker, Ph.D., Josephine Jee
From: William Adams, acting for Sarah Pope Miksinski, Ph.D.
Date: 22 Sep 2010
Re: Final CMC Recommendation for NDA 22-312

NDA 22-312 (Docetaxel Injection) was initially submitted by Apotex, Inc. as a 505(b)(2) application on 28-MAR-2008 and was granted a standard review by the Agency. Chemistry, Manufacturing and Control (CMC) Review #1 (dated 23-APR-2009) identified several CMC deficiencies which were conveyed in a Complete Response (CR) letter dated 28-APR-2009.

The Applicant responded via a complete response submission dated 29-JUL-2009. This resubmission was reviewed in its entirety (CMC Review #2 dated 22-JAN-2010). Container/carton labels were also reviewed by the Division of Medication Errors Prevention and Analysis (DMEPA review finalized 27-JAN-2010). Several DMEPA comments appear to contradict the CMC reviewer's recommendations (see CMC Review #2). Due to the pending action date for this submission, as well as the recommended CR action for the submission, label and labeling deficiencies were deferred to the next review cycle and prior to approval of the NDA. A second CR letter was issued on 29-Jan-2010.

The Applicant responded via a complete response submission dated 24-Mar-2010. This resubmission was revised in its entirety (CMC review #3 dated 17-Sep-2010). Amendments to the application included changes in manufacturing and control sites, protocols for changes to manufacturing sites, and revised labeling. The only unresolved issues are GMP status of the proposed manufacturing and control facilities, and labeling. A third CR letter is to be issued based on facility issues.

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/s/

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, OPS, 301-796-2123

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 13, 2010		22-312		November 24, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection			ASAP

NAME OF FIRM: Apotex, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This amendment provides [redacted] (b) (4) Please review. It is requested that this consult be assigned to Stephen Langille.

This amendment is located in the EDR.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

TESHARA G BOUIE
09/13/2010

From: Tilley, Amy
Sent: Wednesday, August 25, 2010 1:48 PM
To: 'Kiran Krishnan'
Subject: NDA 22312 Docetaxel - Micro Information Request

Importance: High

Kiran,

Below is Micro Reviewers Information Request:

The (b) (4) protocol titled (b) (4) is not acceptable. (b) (4) The applicant is advised to withdraw the (b) (4) protocol until such information can be provided.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

consider the environment before printing this e-mail

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

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/s/

AMY R TILLEY
08/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: PMHS Rosemary Addy			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Amy Tilley/OND/DDOP/301-796-3994	
DATE August 10, 2010	IND NO.	NDA NO. 22312	TYPE OF DOCUMENT Product Insert	DATE OF DOCUMENT August 5, 2010
NAME OF DRUG Docetaxel	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG 5	DESIRED COMPLETION DATE August 18, 2010

NAME OF FIRM: Apotex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DDOP requests PMHS to determine whether the [redacted] (b) (4) This information is needed prior to our label/team meeting to be held on Thursday, August 19, 2010. A copy of the Product Insert received 8-5-10 and this consult will be emailed to Rosemary Addy.

This request is needed by both DDOP and the 505(b)(2) Coordinating Committee in OND.

SIGNATURE OF REQUESTOR Amy Tilley {See appended electronic signature page}	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

AMY R TILLEY
08/10/2010

From: Zimmerman, Paul F
To: "kkrishna1@apotex.com";
cc: Tilley, Amy;
Subject: NDA 22-312 I.R.- Micro
Date: Friday, August 06, 2010 2:25:53 PM

Dear Kiran,

As discussed, we have the following request. Please respond as soon as possible. Please send a return email that you received this.

Please provide the following information regarding the amended (b) (4) protocol titled (b) (4) " submitted to the agency on 23 July 2010.

1. Provide the production cycle parameters to be used for the sterilization of all components and equipment associated with the manufacture of Docetaxel Injection Diluent at the new facility (refer to question 3a of the 14 July 2010 information request).

2. Provide the following information regarding the (b) (4) stoppers to be used for Docetaxel Injection Diluent at the new manufacturing facility.

a. The source of the stoppers

b. The facility at which the stoppers are to be (b) (4)

c. The procedure and acceptance criteria for depyrogenation of the stoppers

d. The procedure and acceptance criteria for container closure integrity testing (e.g. microbial or dye ingress testing) of units packaged with the (b) (4) stoppers.

Thanks
Paul for Amy

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

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/s/

PAUL F ZIMMERMAN
08/06/2010

From: Tilley, Amy
Sent: Thursday, July 29, 2010 4:16 PM
To: 'Kiran Krishnan'
Subject: NDA 22312 PED Exclusivity status update - PI Revisions

Importance: High

Follow Up Flag: Follow up
Due By: Monday, August 09, 2010 12:00 AM
Flag Status: Flagged

Kiran,

After conferring with my chief, since it is the sponsor's responsibility to keep up with patent and exclusivity issues, should your proposed labeling need to be revised please resubmit. We will need your revised PI officially by August 6, 2010.

Also include a side by side comparison to the RLD and include a justification for any differences.

Thanks.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
07/29/2010

From: Tilley, Amy
Sent: Wednesday, July 14, 2010 10:16 AM
To: 'Kiran Krishnan'
Subject: NDA 22312 Docetaxel - Micro Information Request

Importance: High

Kiran,

The Microbiology Reviewer has requested that Apotex address the following product Quality Microbiology Deficiencies related to (b) (4) protocol V-3362:

1. **Amend the title and objective sections of the comparability protocol to reflect the fact that the proposed change applies to the manufacture of diluent for docetaxel injection.**

2. **Upon successful completion of the studies described in this Comparability Protocol, the applicant should report the implementation of manufacturing in the modified facility by submitting a Special Report [21 CFR 314.81(b)(3)(ii)] to the affected applications. The Special Report should reference this approved Comparability Protocol and indicate that they are implementing manufacturing in the modified facility after completing the validation studies agreed to in the Comparability Protocol. Data need not be provided in the Special Report. Validation data should not be submitted as a changes being effected (CBE) supplement.**

3. **Provide the following information for the sterilization and sterilization/depyrogenation cycles for equipment and components:**

    a. **detailed validation and production cycle parameters (time and temperature)** (b) (4)

    b. **a commitment to conduct three sequential successful validation cycles for each load or sterilization process**

    c. **a list of the types of equipment, components and loads to be sterilized**

    d. **a description of the biological indicators to be used (include the population, D-value, source, etc.)**

    e. **a list of the number of biological indicators and thermocouples to be used to monitor validation cycles**

    f. **a description of the location of biological indicator and thermocouple placement for sterilization validation studies and an explanation of**

how the biological indicator and thermocouple placement represents the most difficult to sterilize locations.

4. **Provide confirmation that media-filled units that are positive for growth following incubation will not be discounted if the container closure system is found to be non-integral. Non-integral units should be removed prior to incubation.**

5. **Provide the following information regarding validation and testing of production filters:**

    a. **A detailed summary of the procedure to be used for filter validation testing**

    b. **The method for determining the post-filtration integrity of the production filters**

    c. **Limits for post-filtration integrity testing.**

6. **Provide a detailed description of the environmental monitoring procedures and acceptance criteria to be used at the new facility.**

Please respond to these deficiencies as soon as possible so that the Microbiology Reviewer can adequately complete the review of this application.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
07/14/2010

From: Tilley, Amy
Sent: Friday, May 14, 2010 10:54 AM
To: 'kkrishna1@apotex.com'
Subject: RE: NDA 22312 Docetaxel Injection - Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, June 17, 2010 12:00 AM
Flag Status: Red

Kiran,

On 5/13/10, the Division of Drug Oncology Products approved NDA 020449/supplement 059 Taxotere (docetaxel) Injection (the RLD from Sanofi-Aventis). This label will not be available on our website for a couple of days. Please wait and revise your PI with the label from **5/13/10** (and not the 4/20/10 label) once it appears on our website.

Sorry for any confusion this may have caused you. Also, would you please confirm your receipt of this email.

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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From: Tilley, Amy
Sent: Thursday, May 13, 2010 11:13 AM
To: 'kkrishna1@apotex.com'
Subject: NDA 22312 Docetaxel Injection - Information Request
Importance: High

Kiran,

Since the RLD of Taxotere from Sanofi Adventist has a recently approved PI from 4/20/10 on our website, please revise your PI for this NDA to match that of the RLD. Submit the revised PI officially to this NDA. Please also send me a courtesy email updating me of the date you will be submitting the revised PI.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

consider the environment before printing this e-mail

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

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/s/

AMY R TILLEY
05/17/2010

From: Tilley, Amy
Sent: Thursday, May 13, 2010 11:13 AM
To: 'kkrishna1@apotex.com'
Subject: NDA 22312 Docetaxel Injection - Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, June 17, 2010 12:00 AM
Flag Status: Red

Kiran,

Since the RLD of Taxotere from Sanofi Adventist has a recently approved PI from 4/20/10 on our website, please revise your PI for this NDA to match that of the RLD. Submit the revised PI officially to this NDA. Please also send me a courtesy email updating me of the date you will be submitting the revised PI.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
05/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312 **INFORMATION REQUEST**

Apotex Corp.
US Agent for Apotex Inc.
Attention: Kiran Krishnan
Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Mr. Krishnan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL.

We also refer to your March 24, 2010, submission in response to the FDA Complete Response and to your April 23, 2010, submission. We have the following comment and requests for additional information. Please submit your response no later than Friday, April 30, 2010.

1. In reference to your April 23, 2010, submission, we note that Apotex Inc., 4100 Weston Road has never been proposed as a site for drug product manufacture or testing. Identify the specific responsibilities for this proposed site.

2. Submit a revised appendix for all proposed manufacturing and testing establishments as a continuation to you 356h Form. Include a statement that this information for manufacturing establishments supersedes all previously submitted.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

Sarah Pope Miksinski
04/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312 **INFORMATION REQUEST**

Apotex Corp.
US Agent for Apotex Inc.
Attention: Kiran Krishnan
Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Mr. Krishnan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL.

We also refer to your March 24, 2010, submission in response to the FDA Complete Response Letter dated January 29, 2010. We have the following comments and requests for information. Please submit your response no later than Friday, April 23, 2010.

1. Identify the specific tests to be performed by (b) (4) Include the acceptance testing of drug substance, excipients and packaging components, and the release and stability testing of finished drug product. For each testing facility, identify the analytical methods to be used.

2. Identify the test data generated at each of the testing facilities which have been withdrawn from the application since the original submission. Include material acceptance, product release and stability testing.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

Sarah Pope Miksinski
04/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Liang Zhou through Debbie Mesmer, Office of New Drug Quality Assessment, 301 796-4023

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 20, 2010		022312	NDA- class 2 resubmission	March 24, 2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection	505(b)(2) resubmission-6 month clock	oncology	June 24, 2010

NAME OF FIRM: Apotex Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: ONDQA/DDOP is requesting to have a microbiology review of Apotex Inc's resubmitted NDA 22312, Docetaxel injection. This is a 505(b)(2) and a class 2 resubmission.

Link to application: \\CDSESUB1\EVSPROD\NDA022312\022312.enx

Josephine Jee is the primary CMC reviewer. (Liang Zhou is the PAL.)
Amy Tilley is the OND RPM
Debbie Mesmer is the ONDQA RPM

Please notify Debbie Mesmer of the assigned reviewer. Thank you.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

{See appended electronic signature page}	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DEBORAH M MESMER
04/20/2010

LIANG ZHOU
04/21/2010

Memorandum

To: NDA 22-312

CC: Haripada Sarker, Ph.D., Josephine Jee

From: Sarah Pope Miksinski, Ph.D.

Date: 1/27/2010

Re: Final CMC recommendation for NDA 22-312

NDA 22-312 (Docetaxel Injection) was initially submitted as a 505(b)(2) application on 28-MAR-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 23-APR-2009) identified several Chemistry, Manufacturing and Controls (CMC) deficiencies which were conveyed in the 28-APR-2009 action letter. The Applicant responded via a complete response submission dated 29-JUL-2009.

The 29-JUL-2009 submission was reviewed in its entirety (see Chemistry Review #2 dated 22-JAN-2010). Container/carton labels were also reviewed by the Division of Medication Errors Prevention and Analysis (DMEPA, see review finalized on 27-JAN-2010). Several DMEPA-generated comments appear to contradict the CMC reviewer's recommendations (see Chemistry Review #2). Internal discussion was not possible due to the timing of the review. Therefore, due to the pending action date for this submission, as well as the recommended "Complete Response" action for the submission, CMC recommends that all container/carton and PI labeling deficiencies be deferred during this review cycle. This recommendation was made in consultation with the clinical division.

Labeling deficiencies captured in both reviews will need to be revisited during a subsequent review cycle and prior to approval of this NDA.

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

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/s/

Sarah Pope Miksinski
01/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312

ACKNOWLEDGE CLASS 2 RESPONSE

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Associate Director, Regulatory Affairs

Dear Mr. Krishnan:

We acknowledge receipt on July 29, 2009, of your July 29, 2009, resubmission to your new drug application for Docetaxel Injection (b) (4) 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL).

We consider this a complete, class 2 response to our April 28, 2009, action letter. Therefore, the user fee goal date is January 29, 2010.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

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/s/

CHRISTY L COTTRELL
01/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE/DMEPA
Attention: Sandra Griffiths

FROM: Division of Drug Oncology Products, HFD-150
Christy Cottrell, RPM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 8, 2009		22-312	Class 2 Resubmission	July 29, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection			December 8, 2009

NAME OF FIRM: Apotex, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ✓ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the resubmitted Carton and Container labeling to determine whether the sponsor has adequately addressed DMEPA's comments from the prior review cycle. The submission can be found in GlobalSubmit Review under sdn 011 dated July 29, 2009. PDUFA date is January 29, 2010. Target action date is January 15, 2010. Request completed DMEPA review by December 8, 2009.

Prior DMEPA reviewers were: Loretta Holmes, Kristina Arnwine

For questions, please contact Christy Cottrell at 6-4256.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Christy Cottrell	✓ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

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/s/

CHRISTY L COTTRELL
10/08/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Haripada Sarker through Debbie Mesmer, Office of New Drug Quality Assessment, 301 796-4023

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 2, 2009		22-312	505(b)(2) NDA resubmission	Dated 7/29/09; received 7/30/09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection	Standard		PDUFA date: January 29, 2010

NAME OF FIRM: Apotex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: ONDQA/DDOP is requesting to have a microbiology review of Apotex's resubmitted NDA 22-312 for Docetaxel injection for multiple proposed oncology indications.

Link to application: \\CDSESUB1\EVSPROD\NDA022312\022312.enx

Josephine Jee is the primary CMC reviewer. (Haripada Sarker, PAL)
Qin Ryan is the medical reviewer
Christy Cottrell is the OND RPM
Debbie Mesmer is the ONDQA RPM

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

{See appended electronic signature page}	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

DEBORAH M MESMER
09/02/2009

HARIPADA SARKER
09/03/2009

From: Cottrell, Christy L.
Sent: Tuesday, August 11, 2009 10:53 AM
To: 'Kiran Krishnan'
Subject: NDA 22-312 for Docetaxel Injection: Request for Information

Importance: High

Mr. Krishnan,

Please refer to your July 29, 2009, response to the April 28, 2009, Complete Response letter for NDA 22-312 (Docetaxel Injection). As requested by the nonclinical reviewer, please provide the following references mentioned on page 5 of 10 of your cover letter or direct us to their location in the submission.

References:

1. Farina,Vittorio (editor) The Chemistry and Pharmacology of Taxol and Its Derivatives, Pharmaco
Chemistry Library Volume 22 , Amsterdam, Elsevir, 1995
2. Kingston, D.G.I. Pharmacol. Ther. 1991, 52, 1.
3. Vuilhorgne,M;Gaillard,C;Sanderink,G.J;Monsarrat,B;Dubois.J;Wright,M;Royer,I. *207th Amer.Chem.Soc.Meeting*, 1994;San Diego (abstract)
4. Ringel, I; Horwitz, S.B. J.Pharmacol. Exp. Ther. 1987

Feel free to contact me if you have any questions.

Regards,
Christy Cottrell

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
08/11/2009

Memorandum

To: NDA 22-312

CC: Haripada Sarker, Ph.D., Sharmista Chatterjee, Ph.D., Rik Lostritto, Ph.D.

From: Sarah C. Pope, Ph.D.

Date: 4/28/2009

Re: Final CMC recommendation for NDA 22-312

NDA 22-312 (Docetaxel Injection) was initially submitted as a 505(b)(2) application on 28-MAR-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 23-APR-2009) identified several Chemistry, Manufacturing and Controls (CMC) deficiencies which should be conveyed in the action letter. Of particular note is the cross-referenced Type II Drug Master File (DMF) (b) (4), which was reviewed on 22-APR-2009 and was determined to be inadequate in support of this NDA. While DMF (b) (4) is not mentioned in the overall CMC Recommendation and Conclusion of Approvability (see page 8 of the CMC review for NDA 22-312), the DMF's current deficient status should also be conveyed in the action letter. The deficient status for DMF (b) (4) is captured in the DMF table located on page 6 of the CMC review document.

Resolution of these CMC deficiencies is necessary prior to a CMC recommendation for approval of NDA 22-312. Additionally, at the time of finalization of the 23-APR-2009 CMC review, an overall recommendation from the Office of Compliance had not been received.

This memo serves to update that determination. The Office of Compliance issued an overall withhold recommendation for this application on 27-APR-2009. Accordingly, from a CMC perspective, approval of NDA 22-312 cannot be recommended until the outstanding CMC and compliance deficiencies are adequately resolved.

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/s/

Sarah Pope
4/28/2009 02:00:31 PM
CHEMIST

From: Cottrell, Christy L.
Sent: Monday, April 13, 2009 2:52 PM
To: 'Robin Windover'
Cc: Kiran Krishnan; Bernice Tao
Subject: NDA 22-312 for Docetaxel Injection: Labeling: Response requested

Importance: High
Kiran and team,

We have reviewed your proposed labeling revisions and have accepted them. We have made a couple of minor edits and have a clarification request for Table 3 (see Tracked Changes in the attached document). Please provide your response to these edits and clarification request **by Friday, April 17, 2009**.

In addition, we have the following comments and recommendations pertaining to the carton and container labels:

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) Therefore, delete (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).

2. Diluent

a. The diluent labels contain the Docetaxel Injection (b) (4) statement (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) 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 (i.e., "See package insert...") 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:

Please note that all labeling negotiations are considered preliminary until an action has occurred. Agreement on labeling does not necessarily predict the type of action letter you will receive.

Feel free to contact me if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA

10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov
consider the environment before printing this e-mail

From: Robin Windover [mailto:rwindove@apotex.com]
Sent: Thursday, March 05, 2009 1:48 PM
To: Cottrell, Christy L.
Cc: Kiran Krishnan; Bernice Tao
Subject: URGENT- Please respond: NDA 22-312 for Docetaxel Injection

Hello Christy,
Further to your email request below we are providing our labeling using the track changes functions.

All of your initial track changes have been accepted, with the following exceptions:

1. Indications for **Gastric Adenocarcinoma (GC)** and **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)** have been retained in the labeling, along with the corresponding information for dosage, studies, etc. in other sections. Track changes have been added (in red) for your acceptance.
We propose to retain this information in our labeling to be inline with our Patent and Exclusivity Statements (as per section 1.3.5.2 of the NDA).

In addition to the above, Section 6 (Adverse Reactions) Tables 10 - 12 have been rounded up to whole numbers to be consistent with other tables in that section (in-line with your initial track changes request for other tables).

(b) (4)

All sections have been renumbered as appropriate to incorporate the above information (this is visible through track changes).

If you have any questions, please feel free to contact us.

Regards,
Robin Windover
Manager
Regulatory Affairs - Richmond Hill
Tel: (905) 508-2364
Fax: (905) 508-2359
See our products online at www.apotex.com

From: Cottrell, Christy L. [mailto:Christy.Cottrell@fda.hhs.gov]
Sent: Friday, February 20, 2009 11:13 AM
To: Kiran Krishnan
Subject: URGENT- Please respond: NDA 22-312 for Docetaxel Injection
Importance: High

Kiran,

Please refer to your NDA 22-312 for Docetaxel Injection. Attached are the Agency's initial labeling edits. Please review. We ask that you accept all the changes in the document, then use the Track Changes function to identify your proposals for further edits. **Please provide your updated labeling by noon on Thursday, 2/26/09.**

We have another internal labeling meeting scheduled for Friday, 2/27, during which we will discuss our CMC edits and any proposed revisions that you will have sent to us next Thursday based on the labeling I am sharing with you today. We would like members of the Apotex team to be available for a brief teleconference following our internal meeting next Friday. If possible, **we would like to be able to call you around 10:30am EST to discuss any labeling concerns and/or outstanding issues**. Please let me know if this works for your team. If not, we'll arrange another time during the following week.

Can you provide an update on the status of the User Fee payment? Also, we are still waiting for a response to our December and January CMC Information Requests. Our reviews cannot be finalized without these responses, and given that we are expediting our reviews to try to wrap up by the end of March, we need these responses ASAP. Please let me know when we can expect to receive them. I am attaching the requests again to this email for your reference.

If you have any questions, feel free to call me.

Regards,
Christy

<<2-20-09 FDA revised Docetaxel labeling to sponsor.doc>> <<CMC request for information.pdf>> <<1-15-09 CMC Info Request.pdf>>

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) ● 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov


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/s/

Christy Cottrell
4/13/2009 02:54:26 PM
CSO

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road, Beltsville, MD 20705-1266
10903 New Hampshire Avenue, Building #22, Silver Spring, MD 20993

To: Kiran Krishnan	**From:** Christy Cottrell
Fax: (954) 349-4233	**Fax:** (301) 796-9845
Phone: (954) 384-3986	**Phone:** (301) 796-4256
Pages, including cover sheet: 2	**Date:** February 12, 2009

Re: NDA 22-312 for Docetaxel Injection (Apotex, Inc.)

Mr. Krishnan,

Please refer to Apotex's pending application (NDA 22-312) for Docetaxel Injection. As discussed during our telephone conversation today, our User Fee Staff has brought to our attention that a User Fee should have been paid for this application. Under PDUFA 3, 505(b)(2) applications were exempt from User Fees, however, under PDUFA 4, which became effective in October 2007, all new applications, including 505(b)(2) applications, are required to pay a fee. If new clinical data needs to be reviewed, then a full fee is paid. In your case, however, no new clinical information is being reviewed, therefore, only a half fee is required. We ask that you submit a fee in the amount of $589,000 as soon as possible. Please notify me once your payment has been made. If you have any questions concerning this request, contact Mike Jones at (301) 796-3464.

In addition, our microbiology reviewer has identified a deficiency that must be addressed as soon as possible. See below for details.

- Data should be provided to demonstrate that the initial diluted solution will not support microbial growth during the proposed storage period (refrigerated or at room temperature for 8 hours). Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. http://www.ich.org/cache/compo/276-254-1.html

- Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count, however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.

Finally, we remind you of the outstanding CMC request for information dated January 14, 2009. Please notify me of the anticipated date for submission of your response to that inquiry, as well as the microbiology deficiency above. Submit responses as an amendment to NDA 22-312. If you have any questions, feel free to call me at (301) 796-4256.

Thanks,

Christy Cottrell

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/s/

Christy Cottrell
2/12/2009 12:25:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

INFORMATION REQUEST LETTER

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Associate Director, Regulatory Affairs

Dear Mr. Krishnan:

Please refer to your March 27, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for docetaxel injection, 40 mg/mL.

We also refer to your submissions dated September 17, and December 3, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The approach [redacted] is considered unacceptable. Propose the same set of specification for both release as well as for stability, for both injection concentrate, diluent as well as the initial and final dilutions.

2. Clarify the discrepancy about the impurity identified for the injection concentrate at RRT [redacted] In the original submission this impurity was listed as [redacted] however in the amendments dated September 17 and December 3, 2008, this impurity is listed as [redacted] It is to be noted that [redacted] are two separate impurities, and these two are monitored independently.

3. Comment on your plans to scale up to meet commercial requirements.

4. In the December 3, 2008, amendment, you indicated that the reason for [redacted] Indicate if any processes are in place to [redacted] in the drug product. Furthermore, tighten the specification [redacted] to match with observed release and stability data.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-4256.

Sincerely,

Richard Lostritto, Ph.D.
Director
Office of New Drug Quality Assessment,
Division III
Center for Drug Evaluation and Research

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/s/

Richard Lostritto

1/14/2009 01:40:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

INFORMATION REQUEST LETTER

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Associate Director, Regulatory Affairs

Dear Mr. Krishnan:

Please refer to your March 27, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for docetaxel injection, 40 mg/mL.

We also refer to your submission dated December 3, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

As proposed in the amendment dated December 3, 2008, your proposal (b) (4) is considered unacceptable, since these tests are critical as in-process controls that help to assure overall batch quality.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-4256.

Sincerely,

Sarah C. Pope, Ph.D.
Branch Chief (Acting)
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope

1/21/2009 12:55:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

Apotex, Inc.
c/o Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Associate Director, Regulatory Affairs

Dear Mr. Krishnan:

Please refer to your March 27, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for docetaxel injection, 40 mg/mL.

On December 3, 2008, we received your December 3, 2008, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 28, 2009.

If you have any questions, call me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Christy Cottrell

12/29/2008 11:03:53 AM

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road, Beltsville, MD 20705-1266
10903 New Hampshire Avenue, Building #22, Silver Spring, MD 20993

To: Kiran Krishnan	**From:** Christy Cottrell
Fax: (954) 349-4233	**Fax:** (301) 796-9845
Phone: (954) 384-3986	**Phone:** (301) 796-4256
Pages, including cover sheet: 2	**Date:** December 16, 2008

Re: NDA 22-312 for Docetaxel Injection (Apotex, Inc.)

Mr. Krishnan,

Please refer to Apotex's pending application (NDA 22-312) for Docetaxel Injection. See below for a request for information from the CMC reviewer.

1. Provide a summary of the methods and results of container closure integrity testing on the packaging systems subjected to the same sterilization, filling, and packaging parameters proposed for the docetaxel concentrate and diluent solutions.

2. Address the following microbiology deficiencies regarding the environmental monitoring procedures used at the Weston and Richmond Hill facilities:

   a) Provide a description of the culture medium and incubation parameters to be used for water testing.

   b) Provide the culture medium and incubation parameters for (b) (4) bioburden testing and a justification for the (b) (4) limit when submission batches showed no growth.

   c) Provide the sampling locations (e.g. gloves, arm, chest) used for personnel monitoring at the Weston facility.

d) Incubation of environmental monitoring samples at 30-35°C for 48 hours may not be sufficient to detect slower growing bacteria and fungi. Please provide data justifying these incubation parameters or consider an additional incubation period at a lower temperature.

3. Address the following microbiology deficiencies [redacted (b) (4)]:

[redacted (b) (4)]

4. Provide the following information regarding [redacted (b) (4)] at the Weston manufacturing facility:

a) A description of the manufacturing equipment to be sterilized

b) Diagrams of loading patterns

c) The sterilization validation study parameters and summaries of the validation study results

Please submit your response as an amendment to NDA 22-312. Your response should be provided as soon as possible, but no later than January 9, 2009. If you have any questions, feel free to call me at (301) 796-4256.

Thanks,
Christy Cottrell

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/s/

Christy Cottrell
12/16/2008 03:49:24 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

Apotex Corp.
US Agent for Apotex Inc.
Attention: Kiran Krishnan
Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Mr. Krishnan:

Please refer to your new drug application (NDA) dated March 27, 2008, received March 28, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL.

We also refer to your submission dated September 17, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submissions and have the following request for information. We request a prompt written response in order to continue our evaluation of your NDA.

1) Tighten the proposed acceptance criteria for drug product impurities in the stability specifications. Also, provide (b) (4) acceptance criteria for impurities in drug product during release versus during stability as noted in the original submission and in the amendment dated September 17, 2008. (b) (4)

2) Clarify the following regarding the stability amendment dated September 17, 2008:

   a) It is noted that the rate (b) (4) in the total impurity level is (b) (4) Provide justification.

   b) Provide a reason for occurrence of (b) (4) for all strengths and all stability configurations.

   c) Clarify why data for the degradant eluting at RRT (b) (4) is not provided in the amendment dated September 17, 2008. Data for this degradant was provided in the original submission.

3) Provide the USAN, the IUPAC name, and the CAS registry number for the drug substance.

4) Clarify whether testing for [redacted] (b) (4) polysorbate 80 and for the acidity of PEG 300 are proposed to be conducted during commercial manufacture. If not, justify.

5) Clarify if the vials are for single-use or multiple-use. If the vials are intended for multiple-use, confirm if an antimicrobial agent is used.

6) Confirm if any [redacted] (b) (4) that could result in the loss of the API.

7) In view of potential interaction of the formulation with the [redacted] (b) (4), indicate if any specialized syringes are needed for transfer of the initial dilution into the infusion bags.

8) There is [redacted] (b) (4) for the 20mg/0.5mL that is packaged in 5mL vials, versus the 80mg/2.0mL that is packaged in 10mL vials. Confirm if this would have any bearing on the stability of the packaged solution.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief (Acting)
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope

9/24/2008 04:00:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 022312/S-000

Apotex Inc.
Attention: Kiran Krishnan, Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326

Dear Kiran Krishnan:

Please refer to your March 28, 2008 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL (20mg/0.5 mL and 80 mg/2 mL).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is January 28, 2009.

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Dillard Woody, Regulatory Project Manager, at (301) 796-4097.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Acting Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Alice Kacuba

6/25/2008 12:44:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE Consults

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Alice Kacuba

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 3, 2008		22-312	New NDA	march 27, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection	Priority	Oncology	November 24, 2008 pdufa date=1-19-09

NAME OF FIRM: Apotex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The purpose of this consult is to request evaluation of the proposed Patient Information Leaflet. The proposed labeling is in the edr.

SIGNATURE OF REQUESTOR
Alice Kacuba

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Alice Kacuba

6/3/2008 12:41:15 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Drug Oncology Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 1, 2008

To: Kiran Krishnan US Agent for Apotex	**From:** Alice Kacuba, R.N., MSN, RAC Acting Chief, Project Management Staff Alice.Kacuba@fda.hhs.gov
Company: Apotex Corp	Division of Drug Oncology Products
Fax number: 954-349-4233	**Fax number:** 301-796-9845
Phone number: 954-384-3986	**Phone number:** (301) 796-1381

Subject: Information Request for NDA 22-312

Total no. of pages including cover: _____

Ms. Krishnan,

The purpose of this Information Request is to request clarification:

Do you intend to propose a tradename for NDA 22-312, docetaxel?

Thank you.
Alice Kacuba

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/s/

Alice Kacuba

6/1/2008 08:07:31 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Drug Oncology Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 24, 2008

To: Kiran Krishnan US Agent	**From:** Alice Kacuba, R.N., MSN, RAC Acting Chief, Project Management Staff Alice.Kacuba@fda.hss.gov
Company: Apotex Corp.	Division of Drug Oncology Products
Fax number: 954-349-4233	**Fax number:** 301-796-9849
Phone number: 954-384-3986	**Phone number:** (301) 796-1381

Subject: NDA 22-312

Total no. of pages including cover: _____

Dear Ms. Krishnan,

In reviewing your pending NDA, NDA 22-312, we have the following information requests:

Regulatory
Please address PREA.

CMC
Provide updated stability data for the drug product by the mid cycle of NDA review. Submit the data in electronic format such as SAS transport or Excel spreadsheet and statistical analysis of all stability-indicating quality attributes. Any delayed submissions may not be reviewed in a timely manner to compute a reasonable product expiry.

Please submit a response as an amendment to your NDA.
Feel free to contact me with any questions.

Thank you.
Alice Kacuba

Alice Kacuba, RN, MSN, RAC
(Acting) Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-1381
(f)301-796-9849
alice.kacuba@fda.hhs.gov

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/s/

Alice Kacuba

5/24/2008 05:06:13 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Micro			FROM: Division of Drug Oncology Products/Alice Kacuba, (301) 796-1381	
DATE 5-24-08	IND NO.	NDA NO. 22-312	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 3-26-08
NAME OF DRUG Docetaxel Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE November 24, 2008 Pdufa date-1-19-09

NAME OF FIRM: Apotex

REASION FOR REQUEST

I. GENERAL

NEW PROTOCOL
 PROGRESS REPORT
 NEW CORRESPONDENCE
 DRUG ADVERTISING
 ADVERSE REACTION REPORT
 MANUFACTURING CHANGE/ADDITION
 MEETING PLANNED BY

 PRE--NDA MEETING
 END OF PHASE II MEETING
 RESUBMISSION
 SAFETY/EFFICACY
 PAPER NDA
 CONTROL SUPPLEMENT

 RESPONSE TO DEFICIENCY LETTER
 FINAL PRINTED LABELING
 LABELING REVISION
 ORIGINAL NEW CORRESPONDENCE
 FORMULATIVE REVIEW
 OTHER *(SPECIFY BELOW)*:
New NDA

COMMENTS/SPECIAL INSTRUCTIONS:

Background: The purpose of this consult is to request a review of the appropriate sections of the NDA for an Injectable drug product. This NDA is totally electronic and is in the edr.

CMC reviewer =Sharmista Chatterjee. PAL=Hari Sarker.

Thank you for your assistance.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) MAIL XXXX HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba

5/24/2008 05:55:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC, _____

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Alice Kacuba

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 24, 2008		22-291	New NDA	March 27, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)	_____	Oncology	November 24, 2008 pdufa date=1-19-09

NAME OF FIRM: Apotex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The purpose of this ocnsult is to request evaluation of the proposed labeling. I will invite you to labeling meetings. The proposed labeling is in the edr under the March 27, 2008 submission.

SIGNATURE OF REQUESTOR
Alice Kacuba

METHOD OF DELIVERY (Check one)
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PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

Alice Kacuba

5/24/2008 05:42:27 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Alice Kacuba, DDOP, HFD-150

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 24, 2008		22-312	new NDA	March 27, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Docetaxel Injection 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)g	_____	Oncology	November 24, 2008 pdufa date=1-19-09

NAME OF FIRM: Apotex

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request evaluation of the proposed tradname for NDA 22-312-Docetaxel. The proposed labeling and labels are in the edr under the March 27, 2008 submission.

PDUFA DATE: 1-19-09
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-312
HFD-150/Division File
HFD-150/RPM
HFD-150/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Alice Kacuba 6-1381	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

APPEARS THIS WAY ON ORIGINAL

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/s/

Alice Kacuba

5/24/2008 05:39:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

NDA ACKNOWLEDGMENT

Apotex Corp-Florida
Attention: Kiran Krishnan, US Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Mr. Weston:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Docetaxel Injection, 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL)

Date of Application: March 27, 2008

Date of Receipt: March 28, 2008

Our Reference Number: NDA 22-312

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 27, 2008 in accordance with 21 CFR 314.101(a).

Information Request: Please submit one of the options for PREA: waiver request, deferral request, pediatric data. If already submitted, please provide the location.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Alice Kacuba,RN, MSN, RAC
Acting Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Alice Kacuba

5/24/2008 04:24:26 PM

IND 78,376, Docetaxel Injection
Advanced Solid Tumors
Pre-NDA Meeting
FDA Pre-Meeting Comments

Background:

The purpose of this meeting according to the sponsor is, the Apotex Docetaxel Injection will be submitted as a 505(b)(2) application as there is a qualitative difference in the final infusion solution compared to Taxotere, with the incorporation of PEG-300 ingredient."

Sponsor's Questions:

a) Does FDA agree with Apotex's assessment that a clinical study in support of the 505(b)(2) application for docetaxel injectable is not required?

FDA: Yes.

b) If clinical studies should be required, what type of studies does the FDA require?

FDA: See above.

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/s/

Frank Cross
9/27/2007 03:24:19 PM
CSO