CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312

COMPLETE RESPONSE

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

Attention: Kiran Krishnan
Director, Regulatory Affairs

Dear Mr. Krishnan:

Please refer to your New Drug Application (NDA) dated November 12, 2010, received November 15, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL).

The November 12, 2010, submission constituted a complete response to our September 22, 2010, action letter.

We also acknowledge receipt of your amendments dated December 10, 2010, and January 27 and May 3, 2011, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the Apotex (Toronto, Canada) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Anthony J. Murgo, M.D., M.S.
Acting Deputy 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/

ANTHONY J MURGO
05/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312

COMPLETE RESPONSE

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

Attention: Kiran Krishnan
Associate Director, Regulatory Affairs

Dear Mr. Krishnan:

Please refer to your New Drug Application (NDA) dated March 27, 2008, received March 28, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL).

We acknowledge receipt of your amendments dated November 24, 2009; January 15; March 24; April 23 and 29; June 4 and 17; July 23; August 12 and 31, 2010.

The March 24, 2010 submission constituted a complete response to our January 29, 2010 action letter.

We also acknowledge receipt of your amendment dated August 5, 2010, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

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

PRODUCT QUALITY

The proposed established name "Docetaxel Injection (b) (4)" is not acceptable in that (b) (4) is not a recognized name by the United States Pharmacopeia. We recommend that

you revise your established name to "Docetaxel Injection" in the package insert, container labels, and carton labels.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Please submit draft carton and container labels revised as follows:

Container Labels

A. Active Drug

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

b. Add the statement "For Intravenous Infusion Only After Final Dilution" and place it below the statement "Before Initial Dilution" on the principal display panel. Consider deleting [redacted] (b) (4) to provide additional space, if needed.

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

B. Diluent

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

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

Carton Labels:

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

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

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994.

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

ENCLOSURE:
Carton and Container Labels

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

---

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

/s/

ANTHONY J MURGO

09/22/2010

Anthony J. Murgo, M.D. signing for:
Robert L. Justice, M.D., M.S.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022312 **COMPLETE 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:

Please refer to your new drug application (NDA) dated July 29, 2009, received July 29, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection (b) (4) 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL).

We acknowledge receipt of your amendments dated August 14 and September 10, 2009.

The July 29, 2009, amendment constituted a complete response to our April 28, 2009, action letter.

We also acknowledge receipt of your amendments dated November 24, 2009, and January 15, 2010, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

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

2. Your (b) (4) protocol submitted in the July 29, 2009, amendment (b) (4) is inadequate based on the Microbiology evaluation. Refer to the Microbiology deficiencies below.

CMC MICROBIOLOGY

Although a (b) (4) protocol does not require the inclusion of data, sufficient detail regarding the manufacturing process, the methods by which validation studies will be conducted, and the acceptance criteria for validation studies should be provided prior to approval of the (b) (4) protocol. The following is a list of information required for approval of a (b) (4) protoco (b) (4)

(b) (4)

(b) (4)

LABELING

Submit draft labeling that incorporates revisions in the attached package insert. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

We reserve comment on the proposed container and carton labeling until the application is otherwise adequate.

FACILITY INSPECTIONS

During a recent inspection of the Apotex, Inc. (Etobicoke and Toronto, Canada) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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

Enclosure: Labeling

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

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

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

/s/

ANTHONY J MURGO

01/29/2010

Anthony J. Murgo, M.D. signing for:
Robert L. Justice, M.D., M.S.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-312

COMPLETE 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:

Please refer to your new drug application (NDA) dated March 27, 2008, received March 28, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 40 mg/mL (20 mg/0.5 mL and 80 mg/2 mL).

We acknowledge receipt of your amendments dated September 17, December 3, 2008, March 5, and 12 (3), 2009.

We also acknowledge receipt of your amendment dated March 31, 2009, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

NONCLINICAL

Your proposed acceptance criteria for the following impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%.

Furthermore, you will need to demonstrate that (b) (4) in your drug product both during release as well as during stability is below the ICH Q3B(R2) proposed limit of 0.2%.

Impurity specifications that (b) (4) qualification limit must be lowered to meet the current ICH Q3B(R2) guidance or the impurities will need to be qualified in nonclinical toxicology studies.

Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

PRODUCT QUALITY

DMF (b) (4) is currently inadequate to support your NDA. Deficiencies have been communicated to the DMF Holder; these deficiencies need to be adequately resolved.

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

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

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

Also note the following two comments regarding your application:

- Given the breadth of information provided in the March 31, 2009 amendment, as well as the timing of the submission, this amendment was not reviewed during this cycle.

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

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated 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.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Please submit draft labeling revised as follows:

Package Insert, Container and Carton Labeling

1. In the package insert, the drug name is Docetaxel Injection, however, on the container and carton labeling, the drug name is Docetaxel Injection [redacted] Please clarify the proposed drug name.

2. The [redacted] is too prominent on the labels. Decrease the prominence [redacted] by decreasing its size. Alternatively, delete [redacted].

Container Labels

3. 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 [redacted] 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. [redacted] Therefore, delete [redacted] from the 20 mg/0.5 mL labels and labeling.

   c. The statement of strength [80 mg/2 mL (40 mg/mL)] is not presented in accordance with USP recommendations for the labeling of injectable drug products. According to the USP recommendations: *"For single dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses."*

      The following is the recommended presentation: position the drug concentration (40 mg/mL) immediately beneath the total drug content statement (80 mg/2 mL) and decrease its size so that it has less prominence (see example below).

80 mg/2 mL (40 mg/mL)

4. Diluent

   a. The diluent labels contain the Docetaxel Injection [redacted] statement [redacted] 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 [redacted] Revise the statement to "Diluent for Docetaxel Injection [redacted] 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 [redacted] and provide specific instructions for use of the diluent on the principal display panel, specifically highlighting the quantity to be used for dilution.

Carton Labeling

5. See Comments B-1-b and B-1-c, above, that concern the statements of strength.

6. 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".

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

STATEMENT OF STRENGTH Before Initial Dilution* *see side panel for concentration Obtained after initial dilution step

FACILITY INSPECTIONS

During a recent inspection of the Apotex, Inc. (Etobicoke, Canada) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. An additional manufacturing site (Apotex, Inc., Toronto, Canada) was also determined to be unacceptable. Satisfactory resolution of any related deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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

Enclosure

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

---

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

/s/

Anthony Murgo
4/28/2009 02:54:38 PM
Signing for: Robert L. Justice, M.D., M.S.