

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203551Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203551

SUPPL #

HFD #

Trade Name N/A

Generic Name Docetaxel Injection Concentrate, 20 mg/mL

Applicant Name Actavis Inc.

Approval Date, If Known April 14, 2013

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.

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

Taxotere Injection

NDA#

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

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: Rajesh Venugopal, MPH, MBA

Title: Regulatory Project Manager

Date: February 19, 2013

Name of Office/Division Director signing form: Amna Ibrahim, MD

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

RAJESH VENUGOPAL
04/12/2013

AMNA IBRAHIM
04/22/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203551 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Docetaxel Injection Concentrate Dosage Form: Intravenous		Applicant: Actavis, Inc. Agent for Applicant (if applicable): Donald H. Chmielewski Lachman Consultants
RPM: Rajesh Venugopal		Division: Division of Oncology Products 1
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 20449; Taxotere injection by Sanofi Aventis</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Docetaxel is an abridged hybrid application product. It cross refers to the originator's reference product, Taxotere 40 mg/mL, concentrate and solvent from infusion by Sanofi Aventis. Docetaxel 20 mg/mL concentrate is to be administered as an intravenous solution containing the same active substance as Taxotere with comparable excipients. There is no requirement for bioequivalence testing.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) Taxotere 40 mg/mL, concentrate and solvent from infusion by Sanofi Aventis.</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		

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.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # 20449 and date exclusivity expires: 11-13-13
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # 20449 and date exclusivity expires: 11-13-13
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire 1-3-13
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Draft
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP Action – 03-11-2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X 02-08-2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X 06-07-2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable Taxotere RLD NDA 020449 	X Approved 05-14-1996

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X 01-30-2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X 06-07-2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X 02-08-2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • 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
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 10/19/12 <input checked="" type="checkbox"/> DMEPA 11/21/12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 11/26/12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DPDP 11/26/12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁵/Memo of Filing Meeting) (<i>indicate date of each review</i>) 	X 02-14-2013
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 03-08-2013 <input type="checkbox"/> Not a (b)(2) 03-08-2013
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included - DRAFT
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>505(b)(2) Didn't trigger PREA</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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 (<i>include certification</i>) 	<input type="checkbox"/> Verified, statement is acceptable (N/A)

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Pre-IND meeting on Date unknown
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None N/A
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-15-13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	01-14-2013 Co-signed primary review
• Clinical review(s) (<i>indicate date for each review</i>)	01-14-3013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None N/A
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested N/A

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/28/12 Co-signed primary review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/28/12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None N/A Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested N/A
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None N/A
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 02-22-2013 Co-signed primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 02-22-3013
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 10/17/12 – Approval recommended
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None Bow waiver request granted 11/24/12

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	X 01-14-2013
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 01-08-2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ 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.

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/s/

RAJESH VENUGOPAL
04/12/2013

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Subject: Final Agreed Upon Package Insert
Date: Thursday, February 14, 2013 2:53:00 PM

Hello Don,

The recently submitted (February 8, 2013) and agreed upon package insert does not have the horizontal line that is required to separate the TOC from the Full Prescribing information. Please submit an updated version of the agreed upon labeling with the horizontal line through the gateway as soon as possible.

Thank you,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

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/s/

RAJESH VENUGOPAL
02/14/2013

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Cc: [Kacuba, Alice](#)
Subject: RE: FW: FDA Revised Labeling
Date: Friday, February 01, 2013 1:02:00 PM
Attachments: [1 14 1 3 1 Actavis Package Insert WORD format R3 013013.doc](#)
[image003.png](#)

Hello Don,

We have an additional revision to the PI (see attached in tracked changes). Section 8.4 Pediatric Use should read as follows, "The safety and effectiveness of docetaxel injection concentrate in pediatric patients have not been established."

In addition, DMEPA has the following two additional comments for your response:

1. Switch the positions of the statements "XX mL Single-Use Vial" on the side panel of the container labels with the statement "Cytotoxic Agent". This will increase the prominence and alert the practioners that it is a single use vial.
2. The color you propose for the 80 mg/4 mL strength is similar in color to a currently marketed product with a concentration of 10 mg/mL. After reviewing all of the other docetaxel products currently approved, DMEPA would like to provide guidance on selecting a color that is not similar to other approved docetaxel products that are either two-vial products or products with a concentration of 10 mg/mL. DMEPA is providing a color sample of a currently approved 80 mg/4 mL product. We suggest a color similar to the color sample as it will ensure that there is no overlap with the two-vial products and products that contain a 10 mg/ml concentration. See the sample below:



Pantone 219 C

Please respond by Friday February 8, 2013.

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com

[mailto:D.Chmielewski@Lachmanconsultants.com]

Sent: Wednesday, January 30, 2013 10:43 AM

To: Venugopal, Rajesh

Subject: Re: FW: FDA Revised Labeling

Rajesh,

The submission (Seq 0016) was made this morning at 10:37 am.

Here are the documents in the submission:

(See attached file: 1.1.2 FDA Form 356h.pdf)(See attached file: 1.2 Cover Letter.pdf)(See attached file: 1.14.1.1.1 Label - Vial R2.pdf)(See attached file: 1.14.1.1.2 Label - Carton R2.pdf)(See attached file: 1.14.1.2.1 Annotated Draft Labeling Text - Insert R3.pdf)(See attached file: 1.14.1.2.2 Annotated Draft Labeling Text - Carton R2.pdf)(See attached file: 1.14.1.2.3 Annotated Draft Labeling Text - Vial Label R2.pdf)(See attached file: 1.14.1.3.1 Actavis Package Insert WORD format R3 013013.doc) (See attached file: 1.14.1.3.2 Actavis Package Insert PDF format R3 013013.pdf)(See attached file: 1.14.1.3.3 Actavis Draft Patient Information Text WORD 013013.doc)(See attached file: 1.14.1.3.4 Actavis Draft Patient Information Text PDF 013013.pdf)

If I can get anything else for you, or if there is a problem, please do not hesitate to contact me directly.

Email - or - phone (b) (6)

Donald Chmielewski

Senior Associate

Lachman Consultants

1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)

D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>

To: "D.Chmielewski@Lachmanconsultants.com"

<D.Chmielewski@Lachmanconsultants.com>,

Date: 01/29/2013 12:27 PM

Subject: FW: FDA Revised Labeling

Don,

When my chief and I spoke on the phone with you a couple weeks back, giving you a deadline of January 31 was for the PI changes in addition to the changes you brought up in the email below. So for the email below, you are correct you have until January 31 to respond.

Hope this makes sense.

Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: Venugopal, Rajesh
Sent: Friday, January 18, 2013 3:27 PM
To: 'D.Chmielewski@Lachmanconsultants.com'
Subject: RE: FDA Revised Labeling

Let me re view and get back to you. Did you find supplement 16? Was it ever sent?

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Friday, January 18, 2013 3:13 PM

To: Venugopal, Rajesh
Subject: Fw: FDA Revised Labeling
Importance: High

Rajesh,

Thank you for the telephone call regarding the labeling.

Here is a summary of changes that are in conflict with the labeling revision provided: (as requested in the May 11, 2012 Filing Communication)

The following changes were requested by the agency in their letter dated May 11, 2012 entitled "Filing Communication" but are not incorporated in the track changes document supplied by the agency on Wednesday, January 16, 2013:

1. Highlights section: Addition of 8.4 Pediatric Use

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

2. Addition of the following within the professional labeling:

8.4 Pediatric Use

The safety and effectiveness of docetaxel in pediatric patients have not been established.

3. Addition of "patient information" in the following area:

17. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

(See attached file: FDA Ltr NDA Filed 051112.pdf)

Can you please review this and get back to me as to what we should include in the labeling? Thank you.

Donald Chmielewski
Senior Associate
Lachman Consultants

1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

----- Forwarded by Donald Chmielewski/lcsi on 01/18/2013 03:08 PM -----

From: Donald Chmielewski/lcsi
To: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>,
Cc: "Kacuba, Alice" <Alice.Kacuba@fda.hhs.gov>
Date: 01/18/2013 01:16 PM
Subject: Re: FDA Revised Labeling

Rajesh,

I discussed the labeling review that you provided with Actavis, and they raised a very important issue:

They believe that the Package Insert reviewed was NOT the most recent version submitted on 12/17/12.

They are concerned that if they make corrections according to the review provided, that all issues might not be covered and we will have to go through this again. We need assurance that if the changes provided in the review are all inclusive.

Can you check on this and provide feedback as to whether the changes are all inclusive?

In addition, since Monday is a holiday, and these questions are outstanding, can we get an extension of the date required for the submission? We will provide by January 28th. Is this satisfactory?

Thank you.

Please feel free to call me at (b) (6) or (b) (6) if you need to discuss this further.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc: "Kacuba, Alice" <Alice.Kacuba@fda.hhs.gov>
Date: 01/15/2013 12:39 PM
Subject: FDA Revised Labeling

Hello Don,

We have reviewed the package insert and the patient information document. Please see attached our review and comments of the FDA revised labeling. Please provide your response by Wednesday, January 23.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

[attachment "docetaxel injection concentrate NDA 203551 PPI Jan-2013 marked.docx" deleted by Donald Chmielewski/lcsi] [attachment "DOP1_actavisPI_Jan14_2013.doc" deleted by Donald Chmielewski/lcsi] See our Blog and News/Event Pages!
www.LachmanConsultants.com and click on "Blog" or "News" button.

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/s/

RAJESH VENUGOPAL
02/01/2013

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Subject: NDA 203551 - Label, Labeling, and Packaging Review
Date: Wednesday, January 16, 2013 10:42:00 AM
Attachments: [image005.png](#)
[image006.png](#)

Hello Don,

The Division of Medication Error Prevention and Analysis group has reviewed the labeling and packaging of the study product, Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL. and has requested responses to their additional comments. The comments are provided below. Please respond formally by Friday, January 25, 2013:

1. Due to the availability of multiple formulations of docetaxel in varying concentrations that require different instructions for drug preparation, the potential for confusion among these products is a significant safety concern. Thus, it is essential to differentiate the labels and labeling of these products such that the potential for confusion is minimized. One important feature of the container labels and carton labeling, that may help to differentiate these products, is color. Thus, in an effort to help minimize the potential for confusion that can lead to dosing errors due to similarities or overlaps in color between the products, we take into consideration that colors should not overlap between products with the following characteristics:

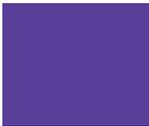
- One-vial vs. two-vial formulations
- Concentration of 10 mg/mL vs. concentration of 20 mg/mL prior to dilution in infusion bag
- Significant strength differences. For example, 20 mg vs. 160 mg

The color you propose for your 20 mg/mL strength is similar to a blue color currently utilized for a product with a significantly different strength. This could lead to confusion between strengths and wrong dose errors. Thus, we request you choose a different color for strength differentiation for your 20 mg/mL product. A sample of the color used by the other docetaxel product that should be avoided is provided below.

Additionally, the color you propose for your one-vial 80 mg/4 mL (20 mg/mL) strength is similar to the color currently utilized for the one-vial 160 mg/16 mL (10 mg/mL) product by Hospira and Sandoz. Thus, we request you choose a color for strength differentiation for your 80 mg/4 mL product that does not overlap with the currently marketed one-vial 160 mg/16 mL Hospira and Sandoz product.

Color samples are provided.



Hospira/Sandoz 160 mg/16 mL: 

2. We note that there are two bar code formats on the container labels. The bar code at the bottom of the PDP appears unnecessary since the NDC bar code is displayed on the side panel. Delete the bar code at the bottom of the PDP or provide your rationale for including it on the container labels. If you provide rationale for including it, please comment on whether it can be decreased in size and relocated to the side panel.
3. On the container labels, please change the statement "Single Use Vial" to read "XX mL Single Use Vial". For example, the 80 mg/4 mL label would read "4 mL Single Use Vial".

Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
01/16/2013

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Cc: [Kacuba, Alice](#)
Subject: FDA Revised Labeling
Date: Tuesday, January 15, 2013 12:38:00 PM
Attachments: [docetaxel injection concentrate NDA 203551 PPI Jan-2013 marked.docx](#)
[DOP1 actavisPI Jan14 2013.doc](#)

Hello Don,

We have reviewed the package insert and the patient information document. Please see attached our review and comments of the FDA revised labeling. Please provide your response by Wednesday, January 23.

Thank you,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

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/s/

RAJESH VENUGOPAL
01/16/2013



NDA 203551

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Lachman Consultants
Attention: Donald H. Chmielewski
Senior Associate
U.S. Agent for Actavis Inc.
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

Please refer to your March 14, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for docetaxel injection concentrate, 20 mg/mL.

On November 13, 2012, we received your November 12, 2012, solicited major amendment to this application. The receipt date is within three 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 14, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 25, 2012.

If you have any questions, call Rajesh Venugopal, Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
12/04/2012

From: Venugopal, Rajesh
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Cc: [Kacuba, Alice](#)
Subject: RE: CMC Information Request of 11/5/12 for Docetaxel 505b2 NDA 203551
Date: Wednesday, November 28, 2012 3:17:00 PM

Don,

Although it is recommended that you revert back to the acceptance criteria for the following attributes that were narrower than those in the USP compendial monograph for Docetaxel drug substance: i.e., Specific Optical Rotation, Heavy metals, Total impurities, Assay, and Bacterial endotoxins, it is acceptable to adopt the USP acceptance criteria for Docetaxel drug substance.

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Wednesday, November 21, 2012 12:31 PM
To: Venugopal, Rajesh
Cc: Kacuba, Alice
Subject: RE: CMC Information Request of 11/5/12 for Docetaxel 505b2 NDA 203551

Rajesh,

The Information Request said:

"Please refer to Agency's drug product comment #2 that was communicated on June 14, 2012 correspondence, you were recommended to "use the USP compendial methods instead of the Ph. Eur. methods for the drug substance and drug product specifications where applicable." Specifically, you were not recommended to change the acceptance criteria to align with the USP monograph for docetaxel if the proposed acceptance criteria are tighter than those of compendial specifications. Please revert back to the acceptance criteria that was originally proposed and that had tighter acceptance criteria for the following parameters: Specific Optical Rotation, Heavy metals, Total impurities, Assay, and Bacterial endotoxins."

We are struggling with a response to this request.

Actavis respectfully asks to retain the USP limits for the Docetaxel API.

Our current API manufacturer, ^{(b)(4)}, has adopted the standard USP limits accordingly.

In addition, ^{(b)(4)}.

We believe that the USP limits will not impact the quality of the API or the resulting FP. Therefore, could the FDA provide rationale why the USP limits are not acceptable for this API?

Can you please ask your CMC reviewers for their comment on this. Thank you.

Donald Chmielewski

Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc: "Kacuba, Alice" <Alice.Kacuba@fda.hhs.gov>
Date: 11/13/2012 03:54 PM
Subject: RE: CMC Information Request #3 for Docetaxel 505b2 NDA 203551

Don,

It was unclear visually where the changes were made to the labeling. We request that you please resubmit all the labeling revisions in tracked changes to help us review. Please send labeling in track changes via email and then send the formal submission via ESG.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Tuesday, November 13, 2012 1:55 PM
To: Venugopal, Rajesh
Subject: RE: CMC Information Request #3 for Docetaxel 505b2 NDA 203551

Rajesh,

Item #5 said to revise the storage conditions.

Therefore, the labeling had to be revised to reflect this change in storage conditions.

That is why labeling was included.

The Annotated Draft Labeling documents - 1.14.1.2.1, 1.14.1.2.2, and 1.14.1.2.3 - show where the changes were made.

The formal submissions were made yesterday via ESG.

Please get back to me if you need more information.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/13/2012 12:56 PM
Subject: RE: CMC Information Request #3 for Docetaxel 505b2 NDA
203551

Hello Don,

I received your amendment 11 submission documents and look forward to the formal submission. Regarding your amendment 12 submission, could you clarify the reason for the label submission? It is not clear where the changes were made to the labels.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [mailto:D.Chmielewski@Lachmanconsultants.com]
Sent: Monday, November 12, 2012 2:02 PM
To: Venugopal, Rajesh
Cc: Kacuba, Alice
Subject: Re: CMC Information Request #3 for Docetaxel 505b2 NDA 203551

Rajesh,

Here are the documents in Amendment 0012 submitted today.

(See attached file: 1.1.2 FDA Form 356h.pdf)(See attached file: 1.2 Cover Letter.pdf)(See attached file: 1.14.1.1.1 label vial R1.pdf)(See attached file: 1.14.1.1.2 label carton R1.pdf)(See attached file: 1.14.1.2.1 annotated-draft-labeling-text R2.pdf)(See attached file: 1.14.1.2.2 annotated draft labeling carton R1.pdf)(See attached file: 1.14.1.2.3 annotated draft labeling vial R1.pdf)(See attached file: 1.14.1.3.1 Actavis Package Insert WORD format R2.doc)(See attached file: 1.14.1.3.2 Actavis Package Insert PDF format R2.doc.pdf)(See attached file: 3.2.R.4.12 validation report-related substances Drug Substance.pdf)(See attached file: 3.2.R.4.13 validation report-ID and assay Drug Substance.pdf)(See attached file: 3.2.R.4.14 validation report-residual solvents Drug Substance.pdf) (See attached file: 3.2.R.4.15 validation report-(b)(4) Drug Substance.pdf)

Unfortunately, we were not able to resolve question #2 by the submission deadline, so we will submit our response as soon as we resolve it.

Thank you.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc: "Kacuba, Alice" <Alice.Kacuba@fda.hhs.gov>
Date: 11/05/2012 10:35 AM
Subject: CMC Information Request #3 for Docetaxel
505b2 NDA
203551

Hello,

Please find attached additional information requests from our CMC group requiring your response. Please respond by no later than November 13, 2012 close of business (5 PM Eastern). If you have questions please let me know.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

[attachment "IR#3 for NDA 203-551 final.doc" deleted by Donald Chmielewski/lcsi] See our Blog and News/Event Pages!
www.LachmanConsultants.com and click on "Blog" or "News" button.

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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/

RAJESH VENUGOPAL
11/28/2012

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Cc: [Kacuba, Alice](#)
Bcc: [Schlick, James](#)
Subject: NDA 203551 - Label, Labeling and Packaging Review
Date: Wednesday, November 21, 2012 2:34:00 PM
Attachments: [image001.emz](#)
[image003.png](#)
[image004.emz](#)
[image005.png](#)
[image006.png](#)
[image007.png](#)

Hello Don,

The Division of Medication Error Prevention and Analysis group has reviewed the labeling and packaging of the study product,

Docetaxel Injection Concentrate 20 mg/mL, 80 mg/4 mL, and 140 mg/7 mL. The following are the group's recommendations.

Please provide the sponsor's response by Tuesday, December 4, 2012.

Thank you,
rajesh

1 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

1. Container Label for the 20 mg, 80 mg and 140 mg Vial
 - a. As proposed, the principal display panel (PDP) occupies approximately two-thirds of the label. A PDP that covers a large horizontal area requires practitioners to rotate the container in order to read the most important information. Redesign the label format so that the established name, product strength, route of administration, and the warning statement "Ready to add..." appear on a PDP that requires no or minimal rotation of the label for a practitioner to read this important information. If space permits, the statement "Single Use Vial" could also appear on the PDP.
 - b. We note that there are two bar code formats on the label. The bar code at the bottom of the PDP appears unnecessary since the NDC bar code is displayed on the side panel. If this bar code is not beneficial for practitioners in the United States, then we recommend removal of this bar code or decrease the size and relocate the bar code to the side panel.
 - c. Decrease the prominence of the statement "Single Use Vial" to minimize distraction with the strength presentation. The statement should appear with a prominence similar to its appearance on the carton labeling. If space is

- limited on the PDP, then this statement may appear on the side panel.
- d. To make room for additional statements to the principal display panel, delete the statement “Sterile, Nonpyrogenic, Preservative-free” since it is also stated on the carton.
 - e. Because the labels are small, remove the ingredients per mL information per 21 CFR 201.10 (h)(2)(i). The ingredient information will be located on the carton labeling to comply with this regulation. This will help minimize distraction from the strength and warning statements discussed in the following recommendations A.1.f-h.
 - f. Change the statement “Ready to add infusion solution” by including the word “to” in the statement to read “Ready to add to infusion solution”.
 - g. Add the statement “For Intravenous Infusion Only” to the principal display panel immediately above the statement “Ready to add to infusion solution”.
 - h. To make room for additional statements on the principal display panel, revise the Usual Dosage and Administration statement to read “See package insert for complete instructions”, and relocate to the side panel.
 - i. Consider changing the statements “Ready to add to infusion solution” to a different font color to improve readability, yet still optimizing the readability of the total drug content and concentration per mL statement on the principal display panel.
 - j. Change “Batch” to “Lot” where the expiration date and lot number will be printed.
2. Container Label for 80 mg and 140 mg Vial
 - a. Relocate the concentration per mL statement “20 mg/mL” on the 80 mg/4 mL and 140 mg/7 mL presentations to just below the total drug content in all places that it appears. Additionally, place the total drug content and “20 mg/mL” statement in the same box with the same color background. Ensure the font size of the per mL concentration is smaller than the font size of the total drug content. Refer to the United States Pharmacopeia General Chapter <1> Injections for additional guidance, if needed.

For example:

- B. Carton Labeling
 1. Add the statement “Contains 1 mL”, “Contains 4 mL”, and “Contains 7 mL” to the appropriate vial carton.
 2. Place the total drug content per vial and the strength per mL “20 mg/mL” statement in the same box with the same color background in each place that it occurs on the carton. Ensure the font size of the per mL concentration is smaller than the font size of the total drug content. See the example in A.2.a for guidance.

3. See A.1.f and A.1.j above and make the appropriate changes to the carton.
 4. Revise the bolded concentration statement “**(20 mg/mL)**” that is located in the box on the side panel with the instructions “Withdraw the required amount of docetaxel...” to a red font color in bold type.
 5. Change the statement “Single Use Vial” to read “Single Use Vial: Discard Unused Portion.” Move this statement to the display on the side panel.
- C. Insert Labeling
1. How Supplied/Storage and Handling – Section 16.1
 - a. Add the strength per mL statement “(20 mg/mL)” immediately after the statement “80 mg/4 mL”.
 - b. Change the statement “140 mg/ mL” to 140 mg/7 mL”. The number “7” is missing. Additionally, add the strength per mL statement “(20 mg/mL)” immediately after the statement “140 mg/7 mL”.

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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

/s/

RAJESH VENUGOPAL
11/26/2012

From: Venugopal, Rajesh
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Cc: [Kacuba, Alice](#)
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551
Date: Thursday, November 08, 2012 8:42:00 AM

Hello Don,

Please provide us with the calculated osmolality for the following formulations by Nov. 13 and submit measured data as soon as possible but no later than 3 weeks (by Nov. 28, 2012).

1. Taxotere U.S. 1 vial,
2. Taxotere U.S. 2 vial,
3. Taxotere E.U. 1 vial,
4. Actavis proposed 1-vial

In addition, we have the following concern regarding the use of povidone K12 in your formulation. Please provide a detailed reply to the following information request by COB 11/21/2012.

1. Provide FDA with examples of any other approved U.S. or European intravenous formulations that contain povidone K12. Provide a copy of the European product label, in English, for any of these products.
2. There have been case reports for anaphylactic reactions related to povidone excipients given topically and intra-articularly. Given we have no clinical data for this docetaxel formulation containing 100mg/mL povidone K12, provide a strong rationale for the safety of this amount of povidone K12 used as an excipient for intravenous infusion.

Garijo et al., Ann Pharmacother. 1996 Jan; 30(1): 37-40.
Ronnau et al., Br J Dermatol, 2000 Nov; 143(5); 1055-8.
Yoshida et al., Int Arch Allergy Immunol. 2008; 146(2): 169-73.
Pedrosa et al., Pediatr Allergy Immunol. 2005 Jun; 16(4): 361-2.

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Wednesday, November 07, 2012 8:59 AM
To: Venugopal, Rajesh
Cc: Kacuba, Alice
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

We cannot meet the timeline of November 12, 2012 if direct testing on all 4 products is required.

The 1 vial Taxotere sourced in US needs to be purchased in the US, and delivered to the Romanian laboratory for testing (this is where the drug product is manufactured - Actavis, Romania). This product was launched on the US market after the submission of the NDA, therefore comparable information was not provided in the submission.

Direct osmolarity testing can be performed in Romania, however the delivery of the RLD is on the critical path.

Scientifically, there is no reason why the osmolarity of the product sourced in US should be different from the one sourced in EU as they have very similar composition. Formulation information was presented in a comparative table between the EU and US composition of the 1 vial Taxotere (in our November 5 amendment), and this together with the calculation of the osmolarity should provide a very strong argument that products in various territories are essentially similar.

The calculation of osmolarity in solution containing non-aqueous solvents is an established method to predict the properties of a product. Data can be provided as evidence that calculated and measured parameters are very close. The calculation method is also used widely in clinical practice.

One other proposal would be to supply as much information as is available on November 12, and submit remaining data when it is available. Otherwise, experimental testing will take 3 weeks to provide all testing results on the 4 injection concentrates.

Please provide us guidance as to how you wish to proceed.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc: "Kacuba, Alice" <Alice.Kacuba@fda.hhs.gov>
Date: 11/06/2012 02:27 PM
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Don,

With respect to question #1 and question #3, a theoretical calculation of the osmolarity is not adequate. Please provide direct testing data for the osmolarity of the following 4 injection concentrates prepared for infusion in both 250mL of D5 water and 250mL of normal saline:

1. Taxotere U.S. 1 vial,
2. Taxotere U.S. 2 vial,
3. Taxotere E.U. 1 vial,
4. Actavis proposed 1-vial

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111

E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Tuesday, November 06, 2012 11:26 AM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Regarding the Clinical Information request, we have a question for #1 and #3.

In response to these questions, can we provide/use only the theoretically calculated osmolarity based on the Taxotere one vial composition stated in the US Sanofi Product Information? Will this information be satisfactory in formulating the response?

Thank you.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 04:37 PM
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA
203551

Thank you for the update.

Rajesh

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 4:33 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Amend 0010 was submitted at 4:28:45 today (11/5/12).

The filing contained the documents that were sent to you earlier today.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:34 PM
Subject: RE: Clinical Information Request for
Docetaxel 505b2 NDA
203551

Ok. Sounds good.

Rajesh

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [mailto:D.Chmielewski@Lachmanconsultants.com]
Sent: Monday, November 05, 2012 1:32 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

I will inform you when I formally submit them through the ESG.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:30 PM
Subject: RE: Clinical
Information Request for
Docetaxel 505b2 NDA
203551

Received. Thank you.

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov

Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 1:24 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Here are the documents for the submission:

(See attached file: 1.1.2 Form FDA 356h.pdf)(See attached file: 1.2 Cover Letter.pdf)(See attached file: 3.2.P.2.2.1.2.10 EMA Scientific Assessment Rpt.pdf)(See attached file: 3.2.P.2.2.1.2.11 Product Information EMA, 2011.pdf)(See attached file: 3.2.P.2.2.1.2.12 Sanofi Aventis US PI Sep 2011.pdf)

Donald Chmielewski
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1600 Stewart Avenue, Westbury, NY 11590 (USA)
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D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:21 PM
Subject: RE: Clinical
Information Request for
Docetaxel 505b2 NDA
203551

Could you provide the response to question #2 via email to me as soon as possible? You can submit the full set of responses to all of our questions through your submission software once it is up and running.

Thank you,

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 12:57 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Thank you for understanding.

I am not giving up on getting it in. I talked by cell to someone at the office, and she said it just went out. So, I am hoping that it will be fixed yet today.

I was in the submission software earlier this morning to set up the amendment. I have the documents ready to load, and will as soon as I can get in.

I will keep you posted.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 12:53 PM
Subject: RE: Clinical
Information Request for
Docetaxel 505b2 NDA
203551

I understand. I grew up on long island, garden city park as a matter of fact. Not too far from your office. My parents don't have electricity or phone connection either. I will update the clinical team on the situation.

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 12:48 PM
To: Venugopal, Rajesh
Subject: Re: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

I've got the submission ready to go, but I am having problems with my home office of Lachman Consultants. They are located on Long Island, where the hurricane hit last week.

The software for the submission is on the server at our office. I am currently having phone problems with Long Island. I did make previous connection with the office today so I hope this is temporary.

If I cannot make the submission, I will get in touch with you later today. I am hoping this is just a temporary problem.

Thank you for your patience.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
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D.Chmielewski@LachmanConsultants.com

From:

"Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To:
"D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc:

"Kacuba, Alice"
<Alice.Kacuba@fda.hhs.gov>
Date:

11/02/2012 02:34 PM
Subject:

Clinical
Information Request for Docetaxel
505b2 NDA
203551

Hello Mr. Chmielewski,

The Clinical Team requests the following:

Please find the following information request for NDA 203551 for docetaxel injection concentrate 20mg/mL. Please provide us with your response to #2 by Monday 11/5/2012. The remainder of the questions should be responded to as soon as possible but no later than COB the following Monday 11/12/2012.

1. Please provide us with an analysis of the osmolarity and components of the 1-vial U.S. Taxotere formulation in both D5W and NS infusion solution.
2. Please provide us with the components of the formulation of the 1-vial E.U. Taxotere formulation for which you have provided us osmolarity data.

3. Provide us with your rationale for why the increased osmolarity of your infusion solutions should not be listed in the warnings section with respect to pain or phlebitis risk given it will be diluted in D5 water in many instances as a standard infusion. (See labeled warning for hypertonic dextrose solutions below). What proportion of the components of the osmolarity in your solution are freely membrane permeable and what is your assessment of the tonicity of your infusional solution in both D5W and NS when compared to the reference Taxotere 1-vial U.S. product?

The following is listed in the Warnings section of the package insert for hypertonic dextrose injections: "Hypertonic dextrose solutions (above approximately 600 mOsmol/liter) may cause thrombosis if infused via a peripheral vein. It is, therefore, advisable to administer such solutions via an intravenous catheter placed in a large central vein, preferably the superior vena cava. Concentrations of Dextrose Injection, USP 20% and greater should be administered exclusively by this route."

The following is listed in the Adverse Reactions section of the package insert for hypertonic dextrose injections: "Too rapid infusion of hypertonic solutions may cause local pain and venous irritation. Rate of administration should be adjusted according to tolerance. Use of the largest peripheral vein and a small bore needle is recommended. (See DOSAGE AND ADMINISTRATION.)"

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
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www.LachmanConsultants.com and click on "Blog" or "News" button.

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/s/

RAJESH VENUGOPAL
11/08/2012

From: Venugopal, Rajesh
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Cc: [Kacuba, Alice](#)
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551
Date: Tuesday, November 06, 2012 2:27:00 PM

Don,

With respect to question #1 and question #3, a theoretical calculation of the osmolarity is not adequate. Please provide direct testing data for the osmolarity of the following 4 injection concentrates prepared for infusion in both 250mL of D5 water and 250mL of normal saline:

1. Taxotere U.S. 1 vial,
2. Taxotere U.S. 2 vial,
3. Taxotere E.U. 1 vial,
4. Actavis proposed 1-vial

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Tuesday, November 06, 2012 11:26 AM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Regarding the Clinical Information request, we have a question for #1 and #3.

In response to these questions, can we provide/use only the theoretically calculated osmolarity based on the Taxotere one vial composition stated in the US Sanofi Product Information? Will this information be satisfactory in formulating the response?

Thank you.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 04:37 PM

Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Thank you for the update.

Rajesh

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 4:33 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Amend 0010 was submitted at 4:28:45 today (11/5/12).

The filing contained the documents that were sent to you earlier today.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b)(6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:34 PM
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA
203551

Ok. Sounds good.

Rajesh

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 1:32 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

I will inform you when I formally submit them through the ESG.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b)(6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:30 PM
Subject: RE: Clinical Information Request for
Docetaxel 505b2 NDA
203551

Received. Thank you.

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 1:24 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

Here are the documents for the submission:

(See attached file: 1.1.2 Form FDA 356h.pdf)(See attached file: 1.2 Cover Letter.pdf)(See attached file: 3.2.P.2.2.1.2.10 EMA Scientific Assesment Rpt.pdf)(See attached file: 3.2.P.2.2.1.2.11 Product Information EMA, 2011.pdf)(See attached file: 3.2.P.2.2.1.2.12 Sanofi Aventis US PI Sep 2011.pdf)

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b)(6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 01:21 PM
Subject: RE: Clinical
Information Request for
Docetaxel 505b2 NDA
203551

Could you provide the response to question #2 via email to me as soon as possible? You can submit the full set of responses to all of our questions through your submission software once it is up and running.

Thank you,

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [mailto:D.Chmielewski@Lachmanconsultants.com]
Sent: Monday, November 05, 2012 12:57 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request for Docetaxel 505b2 NDA 203551

Thank you for understanding.

I am not giving up on getting it in. I talked by cell to someone at the office, and she said it just went out. So, I am hoping that it will be fixed yet today.

I was in the submission software earlier this morning to set up the amendment. I have the documents ready to load, and will as soon as I can get in.

I will keep you posted.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b)(6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Date: 11/05/2012 12:53 PM
Subject: RE: Clinical
Information Request for
Docetaxel 505b2 NDA
203551

I understand. I grew up on long island, garden city park as a matter of fact. Not too far from your office. My parents don't have electricity or phone connection either. I will update the clinical team on

the situation.

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, November 05, 2012 12:48 PM
To: Venugopal, Rajesh
Subject: Re: Clinical Information Request for Docetaxel 505b2 NDA 203551

Rajesh,

I've got the submission ready to go, but I am having problems with my home office of Lachman Consultants. They are located on Long Island, where the hurricane hit last week.

The software for the submission is on the server at our office. I am currently having phone problems with Long Island. I did make previous connection with the office today so I hope this is temporary.

If I cannot make the submission, I will get in touch with you later today.
I am hoping this is just a temporary problem.

Thank you for your patience.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Venugopal, Rajesh"
<Rajesh.Venugopal@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,
Cc: "Kacuba, Alice"
<Alice.Kacuba@fda.hhs.gov>
Date: 11/02/2012 02:34 PM
Subject: Clinical
Information Request for Docetaxel
505b2 NDA
203551

Hello Mr. Chmielewski,

The Clinical Team requests the following:

Please find the following information request for NDA 203551 for docetaxel injection concentrate 20mg/mL. Please provide us with your response to #2 by Monday 11/5/2012. The remainder of the questions should be responded to as soon as possible but no later than COB the following Monday 11/12/2012.

1. Please provide us with an analysis of the osmolarity and components of the 1-vial U.S. Taxotere formulation in both D5W and NS infusion solution.
2. Please provide us with the components of the formulation of the 1-vial E.U. Taxotere formulation for which you have provided us osmolarity data.
3. Provide us with your rationale for why the increased osmolarity of your infusion solutions should not be listed in the warnings section with respect to pain or phlebitis risk given it will be diluted in D5 water in many instances as a standard infusion. (See labeled warning for hypertonic dextrose solutions below). What proportion of the components of the osmolarity in your solution are freely membrane permeable and what is your assessment of the tonicity of your infusional solution in both D5W and NS when compared to the reference Taxotere 1-vial U.S. product?

The following is listed in the Warnings section of the package insert for hypertonic dextrose injections: "Hypertonic dextrose solutions (above approximately 600 mOsmol/liter) may cause thrombosis if infused via a peripheral vein. It is, therefore, advisable to administer such solutions via an intravenous catheter placed in a large central vein, preferably the superior vena cava. Concentrations of Dextrose Injection, USP 20% and greater should be administered exclusively by this route."

The following is listed in the Adverse Reactions section of the package insert for hypertonic dextrose injections: "Too rapid infusion of hypertonic solutions may cause local pain and venous irritation. Rate of administration should be adjusted according to tolerance. Use of the largest peripheral vein and a small bore needle is recommended. (See DOSAGE AND ADMINISTRATION.)"

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products OND/CDER/FDA Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
11/06/2012

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Cc: [Kacuba, Alice](#)
Subject: CMC Information Request #3 for Docetaxel 505b2 NDA 203551
Date: Monday, November 05, 2012 10:35:00 AM
Attachments: [IR#3 for NDA 203-551 final.doc](#)

Hello,

Please find attached additional information requests from our CMC group requiring your response. Please respond by no later than November 13, 2012 close of business (5 PM Eastern). If you have questions please let me know.

Thank you,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

List of CMC comments/information request to be communicated to the applicant:

1. Submit method validation data for the non-compendial methods proposed in the drug substance specifications, i.e. identification (SPM-CD-MP001-08-V*), assay (SPM-CD-MP001-08-V*), related substances (SPM-CD-MP001-06-V*), GC method for residual solvents (SPM-CDMP001-07-V*) and GC method for (b)(4) determination (SPM-CD-MP001-09-V*).

If you will be using the same analytical methods as described in the referenced DMF (b)(4) by the drug substance manufacturer, (b)(4) (DMF holder), you need not have to provide full validation data, but you should clearly state the same in your response and reference the corresponding section of the DMF.

2. Please refer to Agency's drug product comment #2 that was communicated on June 14, 2012 correspondence, you were recommended to "use the USP compendial methods instead of the Ph. Eur. methods for the drug substance and drug product specifications where applicable." Specifically, you were not recommended to change the acceptance criteria to align with the USP monograph for docetaxel if the proposed acceptance criteria are tighter than those of compendial specifications. Please revert back to the acceptance criteria that was originally proposed and that had tighter acceptance criteria for the following parameters: Specific Optical Rotation, Heavy metals, Total impurities, Assay, and Bacterial endotoxins.
3. You did not address Agency's drug product comment #3 that was conveyed to you on June 14, 2012, which reads: "Conduct in-use dilution stability study using the **lowest** drug concentration based on the intended dose". According to the prescribed procedures in section 2.9 (Preparation and Administration) of the package Insert, after dilution in recommended diluent (normal saline or 5% Dextrose) and based on the dose, a final Docetaxel concentration of 0.3 mg/mL to 0.74 mg/mL may be used in the infusion solution for IV administration. Therefore, conduct an in-use dilution stability study using the lowest drug concentration (i.e. 0.3 mg/mL) to support the stability of the diluted drug product.
4. Please note that some of the unknown (b)(4) compounds were detected in your leachable and extractable studies, i.e. (b)(4). However, no safety assessment for the leachables and extractables were provided. Please provide safety data for leachables and extractables that were detected.
5. Based on long term stability study conducted at 25°C/60%RH, it is recommended that you revise the storage condition as follows:
Store at 25°C (77°F), Protect from light

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/s/

RAJESH VENUGOPAL
11/05/2012

#3 of 3

Kacuba, Alice

Subject: Updated: Final Labeling Meeting 505b2NDA 203551 docetaxel injection/Actavis/Kluetz (DOP1) Skarupa

Location: CDER WO 2201 conf rm Bldg22

Start: Wed 11/7/2012 2:00 PM

End: Wed 11/7/2012 3:00 PM

Show Time As: Tentative

Recurrence: (none)

Meeting Status: Not yet responded

Required Attendees: Skarupa, Lisa; Justice, Robert; Ibrahim, Amna; Kluetz, Paul; Maher, Virginia E.; Fourie Zirkelbach, Jeanne; Liu, Qi (CDER); Chen, Wei; Chen, Xiao H; Pope Miksinski, Sarah; Sarker, Haripada; Mesmer, Deborah; Chikhale, Elsbeth G; Fahnbulleh, Frances; Schlick, James; Fuller, Barbara; Wheeler, Chris; Fedenko, Katherine; Jenney, Susan; Palmby, Todd; Chidambaram, Nallaperum; Caulk, Nathan

Optional Attendees: Kacuba, Alice

Resources: CDER 150 Calendar; CDER OODP Announcements; CDER WO 2201 conf rm Bldg22

Alice in OHOP leadership mtg 2-3

Three Labeling Meetings for NDA 203551 (Oct 23, Nov 2, Nov 7)

Sending labeling to Applicant after Final Labeling Meeting.

DRUG: 505b2 Docetaxel Injection concentrate 20 mg/mL

APPLICANT: Actavis Inc.

Proposed Indication: docetaxel is used in the treatment of the following kinds of neoplasm: breast cancer, non-small cell lung cancer; prostate cancer; gastric adenocarcinoma; head and neck cancer.

CDTL: Nallaperum Chidambaram

1. Labeling on Oct 23rd would be NonClinical and ClinPharm
2. Labeling on Nov 2nd would be Clinical and CMC, carton-container
3. Final/Wrap up Labeling on Nov 7th would be Clinical, CMC, other disciplines

Standard Review

PDUFA January 14, 2012

Three labeling meetings to begin September, and ending with labeling negotiations before holidays.

All primary reviews due Dec 10th, secondary review-CDTL review December 17th.

EDR Location: \\CDSESUB1\EVSPROD\NDA203551\203551.enx

For Document Room Staff Use:

Application Type/Number: nda203551
 Incoming Document Category/Sub Category: Electronic_Gateway
 Supporting Document Number: 0
 eCTD Sequence Number: 0000
 Letter Date: 03/14/2012
 Stamp Date: 3/14/2012

#1 of 3

Kacuba, Alice

Subject: FIRSTILabeling Meeting 505b2 NDA 203551 docetaxel injection/Actavis/Kluetz (DOP1)
Skarupa
Location: CDER WO 2201 conf rm Bldg22
Start: Tue 10/23/2012 2:00 PM
End: Tue 10/23/2012 3:00 PM
Recurrence: (none)
Meeting Status: Meeting organizer
Required Attendees: Skarupa, Lisa; Justice, Robert; Ibrahim, Amna; Kluetz, Paul; Maher, Virginia E.; Fourie Zirkelbach, Jeanne; Liu, Qi (CDER); Chen, Wei; Chen, Xiao H; Pope Miksinski, Sarah; Sarker, Haripada; Mesmer, Deborah; Chikhale, Elsbeth G; Fahnbulleh, Frances; Schlick, James; Fuller, Barbara; Wheeler, Chris; Fedenko, Katherine; Jenney, Susan; Palmby, Todd; Chidambaram, Nallaperum; Caulk, Nathan
Optional Attendees: Kacuba, Alice
Resources: CDER 150 Calendar; CDER OODP Announcements; CDER WO 2201 conf rm Bldg22

**Three Labeling Meetings for NDA 203551 (Oct 23, Nov 2, Nov 7)
Sending labeling to Applicant after Final Labeling Meeting.**

DRUG: 505b2 Docetaxel Injection concentrate 20 mg/mL

APPLICANT: Actavis Inc.

Proposed Indication: docetaxel is used in the treatment of the following kinds of neoplasm: breast cancer, non-small cell lung cancer; prostate cancer; gastric adenocarcinoma; head and neck cancer.

CDTL: Nallaperum Chidambaram

1. Labeling on Oct 23rd would be NonClinical and ClinPharm
2. Labeling on Nov 2nd would be Clinical and CMC, carton-container
3. Final/Wrap up Labeling on Nov 7th would be Clinical, CMC, other disciplines

Standard Review

PDUFA January 14, 2012

Three labeling meetings to begin September, and ending with labeling negotiations before holidays.

All primary reviews due Dec 10th, secondary review-CDTL review December 17th.

EDR Location: \\CDSESUB1\EVSPROD\NDA203551\203551.enx

For Document Room Staff Use:

Application Type/Number: nda203551

Incoming Document Category/Sub Category: Electronic_Gateway

Supporting Document Number: 0

eCTD Sequence Number: 0000

Letter Date: 03/14/2012

Stamp Date: 3/14/2012

Scheduled by LS 5/11/12 Reset by LS 9/8/2012

H2Q3

During DDmtg

Kacuba, Alice

Subject: Updated: Second Labeling Meeting 505b2NDA 203551 docetaxel injection/Actavis/Kluetz (DOP1) Skarupa
Location: CDER WO 2201 conf rm Bldg22
Start: Fri 11/2/2012 10:00 AM
End: Fri 11/2/2012 11:00 AM
Recurrence: (none)
Meeting Status: Accepted
Required Attendees: Skarupa, Lisa; Justice, Robert; Ibrahim, Amna; Kluetz, Paul; Maher, Virginia E.; Fourie Zirkelbach, Jeanne; Liu, Qi (CDER); Chen, Wei; Chen, Xiao H; Pope Miksinski, Sarah; Sarker, Haripada; Mesmer, Deborah; Chikhale, Elsbeth G; Fahnbulleh, Frances; Schlick, James; Fuller, Barbara; Wheeler, Chris; Fedenko, Katherine; Jenney, Susan; Palmby, Todd; Chidambaram, Nallaperum; Caulk, Nathan
Optional Attendees: Kacuba, Alice

When: Friday, November 02, 2012 10:00 AM-11:00 AM (GMT-05:00) Eastern Time (US & Canada).
 Where: CDER WO 2201 conf rm Bldg22

~~*~*~*~*~*~*~*~*

Three Labeling Meetings for NDA 203551 (Oct 23, Nov 2, Nov 7)

Sending labeling to Applicant after Final Labeling Meeting.

DRUG: 505b2 Docetaxel Injection concentrate 20 mg/mL

APPLICANT: Actavis Inc.

Proposed Indication: docetaxel is used in the treatment of the following kinds of neoplasm: breast cancer, non-small cell lung cancer; prostate cancer; gastric adenocarcinoma; head and neck cancer.

CDTL: Nallaperum Chidambaram

1. Labeling on Oct 23rd would be NonClinical and ClinPharm
2. Labeling on Nov 2nd would be Clinical and CMC, carton-container
3. Final/Wrap up Labeling on Nov 7th would be Clinical, CMC, other disciplines

Standard Review

PDUFA January 14, 2012

Three labeling meetings to begin September, and ending with labeling negotiations before holidays.

All primary reviews due Dec 10th, secondary review-CDTL review December 17th.

EDR Location: \\CDSESUB1\EVSPROD\NDA203551\203551.enx

For Document Room Staff Use:

Application Type/Number: nda203551
 Incoming Document Category/Sub Category: Electronic_Gateway
 Supporting Document Number: 0
 eCTD Sequence Number: 0000
 Letter Date: 03/14/2012

From: Venugopal, Rajesh
To: D.Chmielewski@Lachmanconsultants.com
Cc: [Kacuba, Alice](#)
Subject: Clinical Information Request for Docetaxel 505b2 NDA 203551
Date: Friday, November 02, 2012 2:33:00 PM

Hello Mr. Chmielewski,

The Clinical Team requests the following:

Please find the following information request for NDA 203551 for docetaxel injection concentrate 20mg/mL. Please provide us with your response to #2 by Monday 11/5/2012. The remainder of the questions should be responded to as soon as possible but no later than COB the following Monday 11/12/2012.

1. Please provide us with an analysis of the osmolarity and components of the **1-vial U.S. Taxotere formulation** in both D5W and NS infusion solution.
2. Please provide us with the components of the formulation of the **1-vial E.U. Taxotere formulation** for which you have provided us osmolarity data.
3. Provide us with your rationale for why the increased osmolarity of your infusion solutions should not be listed in the warnings section with respect to pain or phlebitis risk given it will be diluted in D5 water in many instances as a standard infusion. (See labeled warning for hypertonic dextrose solutions below). What proportion of the components of the osmolarity in your solution are freely membrane permeable and what is your assessment of the tonicity of your infusional solution in both D5W and NS when compared to the reference Taxotere **1-vial U.S. product**?

The following is listed in the Warnings section of the package insert for hypertonic dextrose injections:

"Hypertonic dextrose solutions (above approximately 600 mOsmol/liter) may cause thrombosis if infused via a peripheral vein. It is, therefore, advisable to administer such solutions via an intravenous catheter placed in a large central vein, preferably the superior vena cava. Concentrations of Dextrose Injection, USP 20% and greater should be administered exclusively by this route."

The following is listed in the Adverse Reactions section of the package insert for hypertonic dextrose injections:

"Too rapid infusion of hypertonic solutions may cause local pain and venous irritation. Rate of administration should be adjusted according to tolerance. Use of the largest peripheral vein and a small bore needle is recommended. (See DOSAGE AND ADMINISTRATION.)"

Regards,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products*

OND/CDER/FDA

Bldg. 22, Rm. 6111

E-mail: Rajesh.Venugopal@fda.hhs.gov

Phone: (301) 796-4730

Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
11/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			Environmental Assessment/ Environmental Analysis Review Request	
TO: ENVIRONMENTAL ASSESSMENT STAFF E-mail to: CDER OPS IO EA Paper mail to: WO Bldg 51, Room 4193			FROM: Debbie Mesmer, Project Manager for Quality, ONDQA, DNDQA1	
REQUEST DATE 10/25/12	IND #	NDA 203351	TYPE OF DOCUMENT EA amendment	DATE OF DOCUMENT 9/30/12
NAME OF DRUG Docetaxel Injection Concentrate, 20 mg/mL		PDUFA DATE 14-Jan-13	DATE TO IDENTIFY DEFICIENCIES 11/20/12	DESIRED COMPLETION DATE 11/30/12
NAME OF APPLICANT OR SPONSOR: Actavis Inc.				
GENERAL PROVISIONS IN APPLICATION				
<input checked="" type="checkbox"/> ENVIRONMENTAL ASSESSMENT <input type="checkbox"/> ENVIRONMENTAL IMPACT STATEMENT <input type="checkbox"/> CLAIM OF CATEGORICAL EXCLUSION <input type="checkbox"/> OTHER				
DOCUMENT(S) TO BE REVIEWED (INCLUDE SECTION # OF NDA/IND):				
EDR Link: \\cdsesub5\EVSPROD\NDA203551\0007				
eCTD Sequence Number:				
COMMENTS / SPECIAL INSTRUCTIONS: From the applicant: Regarding the source of the raw material, please be informed that the sources of raw material from all suppliers are grown as private/cultivated plants. Enclosed in this amendment are the Environmental Assessments (EA) from the four suppliers of plants to (b)(4): 3.2.S.2.1.6 (b)(4) – Environmental Assessment 3.2.S.2.1.7 (b)(4) – Environmental Assessment 3.2.S.2.1.8 (b)(4) – Environmental Assessment 3.2.S.2.1.9 (b)(4) – Environmental Assessment These Environmental Assessments document that the source of the raw material is private/cultivated plants.				

SIGNATURE OF REQUESTER:

Deborah Mesmer

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

Version: 11/24/2011

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/s/

DEBORAH M MESMER
10/25/2012

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com
[mailto:D.Chmielewski@Lachmanconsultants.com]

Sent: Monday, October 22, 2012 1:48 PM

To: Skarupa, Lisa

Cc: Venugopal, Rajesh

Subject: RE: Clinical information Request: NDA 203551 Docetaxel
October 19, 2012

Ms. Skarupa,

Thank you for your response.

I will try to get the submission in by 12:30pm tomorrow. If I can't, I will certainly email a preliminary summary.

Donald Chmielewski

Senior Associate

Lachman Consultants

1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)

D.Chmielewski@LachmanConsultants.com

From: "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov>

To: "D.Chmielewski@Lachmanconsultants.com"

<D.Chmielewski@Lachmanconsultants.com> ,

Cc: "Venugopal, Rajesh" <Rajesh.Venugopal@fda.hhs.gov>

Date: 10/22/2012 01:40 PM

Subject: RE: Clinical information Request: NDA 203551 Docetaxel
October 19, 2012

Dear Don,

The Clinical Team had this request.

If you can make it Tuesday COB as a reasonably, thorough research on this topic (osmolarity/phlebitis), that is acceptable.

However, can you email me a 'preliminary' summary by 12:30pm tomorrow?

Sincerely,

Lisa

301-796-2219

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com
[mailto:D.Chmielewski@Lachmanconsultants.com]
Sent: Monday, October 22, 2012 10:59 AM
To: Skarupa, Lisa
Cc: Mesmer, Deborah
Subject: RE: Clinical information Request: NDA 203551 Docetaxel October 19, 2012
Importance: High

Ms. Skarupa,

Yes, I have received the Clinical IR. I have just received the information for the response, and would like to request one extra day to allow for adequate review by appropriate personnel.

I will definitely have the response to you by COB on Tuesday, October 23rd. Is this acceptable?

I would appreciate your allowance for the necessary review of the response.

Thank you.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b)(6)
D.Chmielewski@LachmanConsultants.com

From: "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>, "Mesmer, Deborah"
<Deborah.Mesmer@fda.hhs.gov>
Cc: "Mesmer, Deborah" <Deborah.Mesmer@fda.hhs.gov>
Date: 10/19/2012 10:42 AM
Subject: Clinical information Request: NDA 203551 Docetaxel
October 19, 2012

Dear Donald,

Please see the following Clinical Information Request, please respond by COB Monday October 22nd:

In reference to the 2-fold increase in osmolarity seen with your product when compared with Taxotere, please provide your assessment of the risk for pain, venous irritation or potential thrombophlebitis when administered via a peripheral venous route. Provide literature support for your conclusions if available.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
10/22/2012



NDA 203551

INFORMATION REQUEST

Lachman Consultants
US Agent for Actavis Inc.
Attention: Donald H. Chmielewski
Senior Associate
1600 Stewart Ave
Westbury NY 11590

Dear Mr. Chmielewski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Docetaxel Injection, 20 mg/mL.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response no later than September 24, 2012, in order to continue our evaluation of your NDA.

1. The following comments are for the drug product specification:

You submitted two sets of drug product specification: one for release and one for shelf life. Please confirm whether the two specifications including methods and acceptance criteria are same or not.

In the footnote of the shelf life specification tables, you stated that "acceptance limits for the parameters: coloration, docetaxel assay and related substances will be revised according to the results obtained in the stability studies". This is not acceptable. Delete the aforementioned statement. Please note that shelf life specification is the one that will be considered as a regulatory specification.

In the drug product specification tables, revise the term "Related substances testing" to "Degradation products" per ICHQ6A guidelines.

Please submit updated drug product regulatory specification tables.

2. Several inconsistencies are noted in section 3.2.P.5.6 Justification of Specification, and they are as follows:
 - On page 8 there appears to be something missing after "Bacterial Endotoxins".

- On page 135 there appears to be inconsistency for the proposed acceptance limit for “Bacterial Endotoxins”, which states NMT (b)(4) EU/mg versus NMT (b)(4) EU/mg in the specification table in section 3.2.P.5.1.
 - Also in the table on page 11, the Bacterial Endotoxins limit is indicated as NMT (b)(4) EU/mg. It should be listed as NMT (b)(4)/mg
3. In section 3.2.P.6 Reference Standards or Materials, you stated that ECRS or USP standards are used by the drug product manufacturer whenever available. Clearly indicate which are USP compendial reference standards.
 4. In section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment, you stated that “one industrial batch will be added yearly thereafter, and the stability studies will be conducted in accordance with the approved stability protocol/approved storage conditions”. Since the drug product has three different strengths, annual stability testing should include one batch for each strength with a total of three batches to be tested annually. In addition, provide the post approval stability testing protocol for the annual batches, which consists of testing schedule, storage conditions, and specifications.
 5. We note that the osmolarity of the diluted docetaxel solution (0.74 mg/mL) in 0.9% NaCl and 5% glucose infusion solution is approximately twice that of Taxotere 80 in these two diluents. Please comment on the potential for this higher osmolarity infusion solution to increase the risk for fluid retention including the potential for heart failure exacerbation. This may be of particular concern in the prostate cancer population which often have medical comorbidities.

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

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Branch Chief (Acting), Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
09/12/2012

From: [Mesmer, Deborah](mailto:Mesmer,Deborah)
To: "D.Chmielewski@Lachmanconsultants.com"
Subject: NDA 203551 Docetaxel- Request for information
Date: Tuesday, August 07, 2012 5:14:24 PM

Dear Mr. Chmielewski,

Please refer to NDA 203551 for Docetaxel Injection Concentrate, 20 mg/mL.
We also refer to your submission dated July 27, 2012.

We have the following comments and request for information. Please submit your written response to the NDA no later than **September 7, 2012**.

1. (b)(4) have been identified for use in the manufacture of the subject drug product, (b)(4). Please provide a complete physical description of the alternate (b)(4) as was provided for (b)(4). Also provide the room location for this (b)(4).
2. The production (b)(4) A in validation study VD-08-333-RQ, dated 2010, while the production (b)(4) K, L, M and N in validation study VD-03-378 dated 2011. Since the contents of (b)(4) A are quite different from the contents of (b)(4) K, L, M and N, specifically identify which (b)(4) for the subject drug product Docetaxel Injection Concentrate, 20 mg/ml. Confirm that the total contents of the validation (b)(4) are identical to the total contents of the validation (b)(4). Furthermore, specifically identify only the (b)(4) that contain product contact equipment. Provide specific validation information for (b)(4) pertaining only to the validation of (b)(4) for Docetaxel Injection Concentrate, 20 mg/ml, as necessary.
3. Provide data demonstrating efficiency of endotoxin recovery (% recovery) from the positive controls (b)(4). This information would confirm the theoretical amount of applied endotoxin in the treated samples as well as the ability of the assay to detect endotoxin within a given level of sensitivity.

Please acknowledge receipt of this message, and notify me when you submit your response.

Sincerely,

Deborah Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

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

(301) 796-4023

deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
08/07/2012

From: Mesmer, Deborah
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Subject: NDA 203551 Docetaxel- Request for information
Date: Friday, June 22, 2012 3:07:00 PM

Dear Mr. Chmielewski,

Please refer to NDA 203551. We refer to your email to Deborah Mesmer dated June 22, 2012, requesting clarification of Comment 2 for Drug Product in the FDA Information Request dated June 14, 2012.

We have the following comment:

It is recommended that you use the USP compendial methods instead of the Ph. Eur. methods for the drug substance and drug product specifications, if applicable. Note that some of the Ph. Eur. methods are harmonized with the USP compendial methods. The FDA recommends that you provide comparison between the Ph. Eur. methods and the corresponding USP compendial methods, and explain the significant differences between them.

Sincerely,

Debbie Mesmer

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

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deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
06/22/2012

JANICE T BROWN
06/25/2012

From: [Mesmer, Deborah](#)
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Subject: NDA 203551 Docetaxel- Request for information
Date: Thursday, June 14, 2012 12:39:00 PM
Attachments: [EA Review Requirements for Drugs Derived from Plant Sources.pdf](#)

Dear Mr. Chmielewski,

Please refer to NDA 203551 for Docetaxel Injection Concentrate, 20 mg/mL. We have the following requests for information. Please submit your written response to the NDA no later than July 10, 2012.

-
Drug Substance:

1. Provide the source of the raw material and indicate whether it is grown as a wild plant or cultivated plant. If it is a wild grown plant, you will need to file an Environmental Assessment (EA). If it is cultivated non-wild grown plant, you may claim categorically exclusion under 21 CFR 25.31(a) and/or 21 CFR 25.31 (c). Please refer to the attached FDA document regarding EA Review Requirements for Drugs Derived from Plant Sources.
2. It was noted that in several places in Module 2.3 Quality Overall Summary, you have referred to Module 3.2.S.4.2, Module 3.2.S.4.4, etc. No information has been submitted to Module 3.2.S. Clarify if you are referring to information in Module 3.2.S in DMF

(b)(4)

Drug product:

1. Five excipients used in the drug product formulation comply with Ph. Eur. We recommend that you use USP/NF compendial grade excipients. Alternatively, you may submit an analytical method description, method validation reports, and a comparison between the USP/NF and Ph. Eur. Monographs for those five excipients as well as your justification of selection of the Ph. Eur. grade excipients instead of USP/NF compendial grade excipients.
2. It is recommended that you use the USP compendial methods instead of the Ph. Eur. methods for the drug substance and drug product specifications, if applicable. Alternatively, provide detailed description of the methods and method validation reports for those that are not based on the USP compendial methodology.
3. Conduct in-use dilution stability study using the lowest drug concentration based on the intended dose.
4. Conduct packaging materials extractables/leachables studies using the intended formulation solution to determine the level of the extractables/leachables. Provide justification for the safety for the potential leachables to be present at release and expiry.

Please acknowledge receipt of this message and contact me if you have any questions.

Sincerely,
Debbie Mesmer

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

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deborah.mesmer@fda.hhs.gov

FDA/CENTER FOR DRUG EVALUATION AND RESEARCH

ENVIRONMENTAL ASSESSMENTS / USE OF FLORA

Source: Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (7/1998) <http://www.fda.gov/cder/guidance/index.htm#chemistry>

I. NDA and ANDA APPLICATIONS

a. Cultivated Plants

Actions involving drug or biologic products derived from cultivated plants (e.g., grown in plantations, nursery stock ...) are normally categorically excluded under 21 CFR 25.31(a) and/or 21 CFR 25.31(c).

i. Claims of Categorical Exclusion

To claim a categorical exclusion, the applicant must state 1) that the action requested qualifies for a categorical exclusion, citing the particular categorical exclusion that is claimed, and 2) that to the applicant's knowledge, no extraordinary circumstances exist (see 21 CFR 25.15(d)).

Typically, the following statement is provided:

Applicant's name claims that approval of this (A)NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(x) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from cultivated plants, CDER requests that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., DMF, page number of application):

- (1) biological identification (i.e., common names, synonyms, variety, species, genus and family);
- (2) a statement as to whether wild or cultivated specimens are used;
- (3) the geographic region (e.g., country, state, province) where the biomass is obtained; and
- (4) a statement indicating:
 - (a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
 - (b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party

- (c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
- (d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.

CDER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

b. Non-Cultivated Plants

An Environmental Assessment (EA) is ordinarily required for NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is *derived from plants taken from the wild*. EAs are also ordinarily required for supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance and which will cause more harvesting than what was described in the original EA. The content and format follows.

i. EA Content and Format

This section describes the basic information that should be submitted in an EA for a drug or biologic product derived from plants taken from the wild. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

- a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name), 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

a. Nomenclature

- i. Established Name (U.S. Adopted Name-USAN)
- ii. Brand/Proprietary Name/Tradename
- iii. Chemical Names or Genus/Species of Biologic Product
 - Chemical Abstracts (CA) Index Name (inverted form)
 - Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

a. Use of Resources

Information relating to the source of the plant, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods

and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating:
 - (a) whether the species is determined under the Endangered Species Act (ESA) or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened,
 - (b) whether the species is entitled to special protection under some other Federal law or international treaty to which the United States is a party
 - (c) whether the species is the critical habitat of another species that has been determined to be endangered or threatened under ESA or CITES
 - (d) whether the species is the critical habitat of another species entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of the plant used and whether it is a renewable resource.
- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidance (include citations to applicable regulations or guidance).
- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.
- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided. (*This information may be provided in confidential appendix*).
- An estimate of the total number of plants in the geographic region where the biomass is obtained.
- Any uses of the plant other than for the proposed use (humans, food source, habitat for fauna).

- Plant growth rates and/or life span and, if applicable, the rate of reproduction/regeneration.
- A discussion of whether harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that no mitigation measures are needed.

Discuss mitigation measures for actions involving flora such as mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) (see 40 CFR 1508.20).

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed.

Discuss alternatives for actions involving flora. A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

9. Certification

{Applicant Name} confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under *{Country/State where harvested}* law to date relating to the harvesting of *{plant species}* for *{Applicant Name}*. *{Applicant Name}* commits that it will continue to comply with all requirements under *{Country/State where harvested}* law relating to such harvesting, including

any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well.

10. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's qualifications.

11. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

12. Appendices

Both confidential and nonconfidential appendices can be included. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

EA FORMAT OUTLINE

- 1. Date**
- 2. Name of Applicant/Petitioner**
- 3. Address**
- 4. Description of Proposed Action**
 - a. Requested Approval**
 - b. Need for Action**
 - c. Locations of Use**
 - d. Disposal Sites**
- 5. Identification of Substances that are the Subject of the Proposed Action**
 - a. Nomenclature**
 - i. Established Name (U.S. Adopted Name - USAN)**
 - ii. Brand/Proprietary Name/Tradenname**
 - iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)**
 - **Chemical Abstracts (CA) Index Name**
 - **Systematic Chemical Name**
 - b. Chemical Abstracts Service (CAS) Registration Number**
 - c. Molecular Formula**
 - d. Molecular Weight**
 - e. Structural (graphic) Formula/Amino Acid Sequence**
- 6. Environmental Issues**
- 7. Mitigation Measures**
- 8. Alternatives to the Proposed Action**
- 9. List of Preparers**
- 10. References**
- 11. Appendices**
- 12. Certification**

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/s/

DEBORAH M MESMER
06/14/2012

JANICE T BROWN
06/14/2012



NDA 203551

NDA ACKNOWLEDGMENT

Actavis Inc.
Attention: Donald H. Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

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

Name of Drug Product: docetaxel injection concentrate, 20 mg/ mL

Date of Application: March 14, 2012

Date of Receipt: March 14, 2012

Our Reference Number: NDA 203551

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 13, 2012, in accordance with 21 CFR 314.101(a).

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should 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 Oncology Products 1
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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

LISA M SKARUPA
06/07/2012

From: [Mesmer, Deborah](mailto:Mesmer,Deborah)
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Subject: NDA 203551 Docetaxel- Request for information
Date: Tuesday, May 22, 2012 1:43:00 PM

Dear Mr. Chmielewski,

Please refer to NDA 203551. We have the following requests for information. Please submit your response to the application no later than July 31, 2012.

1. Regarding (b)(4):
 - a. Please provide an explanation for the validation of (b)(4). It appears that this (b)(4) and is not relevant to materials used in the (b)(4) manufacture of the subject drug product. Please refer to (b)(4).
 - b. Indicate how the components of the (b)(4) filling machine (b)(4) are (b)(4) procedures, do not describe this equipment. Please provide validation data as necessary.
2. Regarding the (b)(4), please provide the most recent requalification data for the (b)(4). With these data include endotoxin recovery from the positive controls demonstrating efficiency of recovery of endotoxin from vials that are untreated.
3. Regarding endotoxin testing validation, even though testing is acceptable as performed, the MVD appears to be incorrectly calculated by using an endotoxin limit that is greater than the endotoxin specification for the drug product. Please recalculate the endotoxin testing MVD for the drug product using the maximum allowable endotoxin content as indicated by the product release and stability specifications.

Please acknowledge receipt of this message, and contact me if you have any questions.

Sincerely,

Debbie Mesmer

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
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
05/22/2012

JANICE T BROWN
05/23/2012



NDA 203551

FILING COMMUNICATION

Actavis Inc.
Attention: Donald H. Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

Please refer to your New Drug Application (NDA) dated March 14, 2012, received March 14, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for docetaxel injection concentrate, 20 mg/ mL.

We also refer to your amendments dated March 22, 23, and April 26, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 14, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 14, 2012.

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

PLR FORMAT LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights: Replace “1996” with “XXXX” because we have not yet acted on this NDA, so the initial U.S. Approval year is not yet known. It will be updated once action is made for this NDA.
2. Highlights: Insert “XX” in all references to “Revised: 01/2012”, it will be updated once action is made for this NDA.
3. Cannot omit subsection 8.4 Pediatric Use from the Table of Contents or Full Prescribing Information. When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)

Use this language in subsection 8.4 Pediatric Use in the Full Prescribing Information:
“The safety and effectiveness of docetaxel in pediatric patients have not been established.”

4. Patient Counseling Information: Correct label to include “(Patient Information)”:
“See FDA-approved patient labeling (Patient Information)”

We request that you resubmit labeling that addresses these issues by 3 weeks from date of this letter. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
05/11/2012

From: [Mesmer, Deborah](mailto:Mesmer,Deborah)
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Subject: NDA 203551 Docetaxel- Request for information
Date: Thursday, April 19, 2012 1:07:00 PM

Dear Mr. Chmielewski,

Please refer to NDA 203551. We have the following requests for information. Please provide your response no later than April 25, 2012.

1. According to 21CFR 320.21, your NDA should include either in vivo BE data or a biowaiver request to support the approval of your product. However, we could not locate either of them in your submission. If this information was provided in your NDA, please tell us where specifically it is located in your submission. If not, please submit a biowaiver request (with the supportive data) or the in vivo BE data.
2. Please submit to your application the clarification submitted by email to Deborah Mesmer on April 11, 2012, in response to the FDA information request of the same date regarding container/closure integrity studies.

Please acknowledge receipt of this message and contact me if you have any questions.

Sincerely,

Debbie Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

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

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

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [
mailto:D.Chmielewski@Lachmanconsultants.com]
Sent: Wednesday, April 11, 2012 3:05 PM
To: Mesmer, Deborah
Subject: Re: NDA 203551 Docetaxel- Request for information

Deborah,

I hereby authorize you to send a request for information for NDA 203551 as an email message.

Our company, Lachman Consultants, will be pursuing setting up secure email accounts next month with FDA.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell:  (b)(6)
D.Chmielewski@LachmanConsultants.com

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/s/

DEBORAH M MESMER
04/19/2012



*ed v 3-11-12
203551*

Draft Responses

MEETING DATE: March 25, 2011
TIME: 2:30 p.m-3:30 p.m.
LOCATION: White Oak Bldg 22, conference room 2327
SPONSOR Actavis, Inc.
APPLICATION: PIND 110851
DRUG NAME: Taxotere (Docetaxel 20 mg/mL Injection Concentrate)
TYPE OF MEETING: Pre-IND/Pre-NDA
MEETING FORMAT Teleconference
MEETING CHAIR: Steve Lemery
MEETING RECORDER: Melanie Pierce

TENTATIVE LIST OF FDA ATTENDEES:

Office of Oncology Drug Products

Richard Pazdur Director
Anthony Murgos Acting Associate Director
Tamy Kim Acting Associate Director, Regulatory Affairs

**Office of Oncology Drug Products
Division of Biologic Oncology Products**

Patricia Keegan Director
Joseph Gootenberg Deputy Division Director
Steve Lemery Clinical Reviewer Team Leader
Shan Pradhan Clinical Reviewer
Anne M. Pilaro Pharmacology/Toxicology Supervisor
Mary Jane Masson-Hinrichs Pharmacology/Toxicology Reviewer
Melanie Pierce Regulatory Project Manager

**Office of New Drugs Quality Assessment
Division New Drugs Quality Assessment 1**

Liang Zhou CMC Team Leader
Angela Dorantes Lead Pharmacologist

**Office of Clinical Pharmacology
Division of Clinical Pharmacology V**

Hong Zhao Clinical Pharmacology Team Leader
Stacy Shord Clinical Pharmacology Reviewer

Office of Biostatistics



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

Kun He

Statistical Team Leader

Office of Regulatory Policy
Division of Regulatory Policy I
Janice Weiner

Regulatory Counsel

TENTATIVE LIST OF SPONSOR ATTENDEES:

Terri Nataline

Vice President, Regulatory Affairs and Medical
Affairs, Actavis Inc.

Joann Stavole
Cornelia Stancu

Director, Regulatory Affairs, Actavis Inc.
Director, Regulatory Affairs & Formulation
Development, Actavis Romania

(b) (4)

Director of Science, (b) (4) (Toxicologist)

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BACKGROUND:

On December 17, 2010, Actavis, Incorporated requested FDA's concurrence on the data supporting a 505(b)(2) application for Docetaxel Injection Concentrate. Actavis stated their intention to submit an NDA for Docetaxel 20 mg/mL Injection Concentrate which contains a different active ingredient than Taxotere[®]. The proposed NDA will be based on safety and efficacy data contained in Taxotere[®] NDA 20,449, as well as published literature and additional comparative non-clinical data between Actavis' docetaxel and Taxotere[®]. New data submitted by Actavis include Chemistry, Manufacturing and Control information as well as comparative nonclinical study reports and summary documents.

Actavis stated that they developed a formulation of docetaxel injection which can readily be diluted in intravenous infusion bags without requiring an intermediate step to dissolve the concentrate in a solvent as opposed to Taxotere, which currently uses a one and two vial system of 40 and 20 mg/mL, respectively. Actavis' proposed drug product will be supplied as 20 mg/mL, 80 mg/4 mL, and 140 mg/7mL strengths for further dilution in 5% glucose or 0.9% sodium chloride solution prior to intravenous infusion.

Actavis indicates that pharmacokinetic, bioequivalency (21CFR 314.54(d)(3)) or clinical studies 21 CFR 314.53(d)(5)) are not required to demonstrate safety and efficacy for the modifications made in the proposed docetaxel injection concentrate for the following reasons:

- The difference in polysorbate 80 concentrations between the two formulations is minimal, especially at the final dose stage in infusion bags.
- Though the ethanol concentration in the proposed formulation is higher than the two vial system formulation of Taxotere, it is almost the same as in one vial formulation of Taxotere.
- Two additional inactive ingredients, povidone (Kollidon 12 PF) as a (b)(4) and citric acid as a (b)(4) in the proposed formulation, are commonly used in parenteral formulations and at much higher concentrations. The solubilization of docetaxel, a poorly water-soluble active substance, (b)(4)

Completed Comparative Nonclinical Studies:

Actavis studied pharmacologic activities and toxicological profiles of the two formulations in comparative non-clinical studies. In comparative pharmacology studies, human MX-1 mammary carcinoma (Study #ACTA200801R4) and PC-3 prostate carcinoma (Study #ACTA200802R4 [MIR10471]), xenografts were established in athymic *nu/nu* mice and the animals were treated intravenously with 20 mg/kg of either Actavis' Docetaxel Injection Concentrate or Taxotere every 4 days for 3 doses. Actavis claims that there were no major

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A study to compare the toxicokinetics and toxicity of Actavis' Docetaxel Injection Concentrate following cyclical intravenous infusions to the reference drug Taxotere was conducted in rats (Study no. DVC0002). For each formulation, animals were treated by a 1-hour intravenous infusion on Study Days 1 and 22 with vehicle (control), 2.5, 5 or 10 mg/kg of docetaxel equivalent. Following the final dose, the rats were observed until the end of Study Week 6, and recovery animals were observed until the end of Study Week 9, then necropsied and evaluated for serum biochemistry, hematology, toxicokinetics, and histopathology. Actavis concluded that under the conditions of this study, the toxicological and toxicokinetic profiles of Docetaxel Injection Concentrate and Taxotere were considered to be comparable, and that administration of either test article resulted in changes consistent with the known toxicity of docetaxel.

Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 25, 2011, between Actavis and the Division of Biologic Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Sponsor Submitted Questions and FDA Response:

1. Because Actavis' proposed Docetaxel Injection Concentrate contains Kollidon[®] 12F (a grade of povidone) and citric acid, neither of which is an antioxidant, preservative or buffering agent, an ANDA under Section 505(j) of Federal Food, Drug and Cosmetic Act, is unsuitable. In addition, Actavis intends to include a 140 mg/7 mL vial. Does the FDA agree with Actavis' proposal to submit a NDA for Docetaxel Injection Concentrate under Section 505(b)(2)?

FDA Response: In general, a 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-voll.pdf>).

If Actavis intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, Actavis must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Actavis should establish a "bridge" (e.g., via comparative bioavailability data) between the proposed drug product and each listed drug upon which Actavis proposes to rely to demonstrate that such reliance is scientifically justified. If Actavis intends to rely on literature or other studies for which they have no right of reference but that are necessary for approval, Actavis also must establish that reliance on the studies described in the literature is scientifically appropriate.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before Actavis' application is submitted, such that Actavis' proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, FDA may refuse to file Actavis application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

2. Actavis will base its NDA for Docetaxel Injection Concentrate on the safety and efficacy data of the Taxoterd NDA No. 20,449 and its subsequent safety and efficacy supplements, as well as supporting relevant published literature. The Actavis NDA will contain CMC data and comparative non-clinical study reports that Actavis generated in support of the new formulation. Does the FDA concur with the be overall content of the Docetaxel Injection Concentrate NDA based on Section 505(b)(2) of the FD&C Act?

FDA Response: No. Based on the CMC information provided in this meeting package, FDA is unable to respond to Actavis' question (see additional CMC comments).

3. Actavis' Docetaxel Injection Concentrate 20 mg/mL in a single vial and ready to admix in iv infusion bag, contains Kollidon[®] 12F (a grade of, povidone) as a (b)(4) (b)(4) for docetaxel and citric acid as (b)(4) Actavis" formulation also contains polysorbate 80 and, ethanol, which are present in the

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Taxotere formulation. Because of the differences in excipients used, Actavis performed animal studies to assess whether there were any significant differences between Taxotere and Docetaxel Injection Concentrate. These comparative animal studies did not show any major differences in pharmacological activities, pharmacokinetic properties and toxicity profile. Some of the differences noticed in the repeat dose toxicity studies are within normal variability and potentially due to differences in dosing stress.

- a. Does the FDA concur with Actavis that the differences noticed in animal studies, specifically in the repeat-dose toxicology study, are minor?

FDA Response: There is insufficient information provided in the meeting package for FDA to agree that the differences noted in the nonclinical studies between Taxotere and docetaxel injection concentration are minor. Final determination of the similarity between the nonclinical results with Taxotere® and docetaxel injection concentration will be a review issue at the time of the IND or NDA submission.

- b. Does the FDA agree that no additional nonclinical toxicology study is necessary?

FDA Response: No, FDA does not agree. At the time of the NDA submission, provide nonclinical data that qualify the safety of povidone (Kollidon PF-12) for intravenous use at the concentration present in a dose of 100 mg/m² docetaxel injection concentration (i.e. 810 mg for a 60 kg person with a total body surface area of 1.62 m²). FDA recommends that Actavis conduct a GLP-compliant, 3-month repeat dose toxicology study (e.g. q 2-3 weeks dosing for 6 cycles) with povidone (Kollidon PF-12) in rats at 2 dose levels (the human equivalent dose and a 10-fold higher dose) to establish a safety margin for povidone for intravenous use.

Alternatively, Actavis may provide data from GLP-compliant toxicology studies conducted by the manufacturer of povidone (BASF corporation) by either obtaining a letter of authorization for FDA to cross-reference to an existing FDA IND, NDA or master file (DMF) application on Actavis' behalf, or by providing full study reports in the NDA submission.

- c. Does the FDA concur with Actavis that no comparative human pharmacokinetic or clinical study is needed?

FDA Response: If the Office of New Drug Quality Assessment (ONDQA) states a biowaiver is not permissible, the following comments apply: A nonreplicate crossover human pharmacokinetic comparability study in which subjects receive a single intravenous dose of the proposed or the innovator drug product is recommended. The frequency and duration of blood sampling should

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be sufficient to accurately estimate relevant PK parameters. To establish comparative bioavailability, the 90% confidence interval of the ratios of the geometric means must be within (80% to 125%) range for the AUC_{inf} and the C_{max} of both total and free docetaxel in plasma. The bioanalytical methods must be accurate, precise, selective, sensitive and reproducible as described in the Guidance for Industry: Bioanalytical Method Validation found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

4. In addition to comparative animal studies, Actavis performed micelle studies to assess whether there were any significant differences between Taxotere and Docetaxel Injection Concentrate that might influence the active substance distribution and bioavailability. These studies did not show any major difference in micelle size, distribution and critical micellar concentration. (b)(4) minor increase in critical micellar concentration. This minor increase in critical micellar concentration value of the (b)(4) is not expected to influence formation of micelle aggregates or solubilization properties because of the presence of (b)(4) in the amount that is (b)(4) folds higher than critical micellar concentration.

- a. Does the FDA concur with Actavis that the differences noted in critical micellar concentration are minor?

FDA Response: Based on the CMC information provided in this meeting package, FDA is unable to respond to Actavis' comment on the question. Provide the data and summary of studies to demonstrate that physical and chemical characteristics between Actavis' Taxotere and Docetaxel Injection Concentrate are similar (see additional CMC comment).

- b. Does the FDA concur with Actavis that no human bioavailability study is necessary?

FDA Response: See response to question 3c.

5. A detailed table of contents for the proposed Docetaxel Injection Concentrate NDA following the FD&C 505(b)(2), 21 CFR 314.54 and the ICH guidelines for CTD is provided in Appendix 2 of this briefing document. Actavis intends to electronically submit the application. Does the FDA agree with the overall content and format of the NDA?

FDA Response: Insufficient information was submitted in the briefing package to address NDA content issues at this time.

6. The reports of nonclinical studies performed by Actavis to compare the effectiveness, pharmacokinetics and toxicity of the proposed drug product to Taxotere, as well as relevant published literature will be the overall content of Module 4. This Module will

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also rely on the FDA's findings from Taxotere NDA and relevant subsequent supplements. In addition, available toxicology study results for Kollidon 12 PF performed by its manufacturer, BASF, will also be included in Module 4. Is the overall content for Module 4 acceptable?

FDA Response: See FDA's response to question 4b.

7. The safety and efficacy of Actavis' Docetaxel Injection Concentrate will be based on that established for Taxotere in NDA 20,449 and subsequent approved safety and efficacy supplements. As allowed under Section 505(b)(2), the NDA for Docetaxel injection Concentrate will refer to the Taxotere NDA to establish its safety and efficacy. In addition, the Module 5 will include copies of relevant literature. Does the FDA agree with the proposed content of Module 5?

FDA Response: FDA cannot adequately answer this question because the contents of Module 5 will depend on what information is necessary to support your application. In addition, please refer to our response under question 1 regarding providing justification that reliance on a listed drug and published literature is scientifically appropriate.

8. The proposed Package Insert labeling for Actavis' Docetaxel Injection Concentrate will be almost identical to that of Taxotere except for changes necessary to address a different manufacturer and inactive ingredients. Does the FDA concur?

FDA Response: Insufficient information was submitted in the briefing package to allow the Agency to address labeling at this time.

Additional Chemistry, Manufacturing and Controls Comments:

9. Provide the following CMC information in your meeting package (or by reference to a DMF):
- a. Drug Substance:
 - (1) Reference to Type II DMF for drug substance
 - (2) Name and address of site of manufacturing and controls
 - (3) Specifications
 - (4) Reference standard information
 - b. Drug Product:
 - (1) Manufacturing process and controls, in-process

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- (2) Name and address of manufacturer(s)
- (3) Proposed specification,
- (4) Sterility assurance package
- (5) Propose expiry dating period with supporting stability data

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/s/

MELANIE B PIERCE

03/24/2011