

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203214Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203214

SUPPL #

HFD # 570

Trade Name Xeljanz

Generic Name tofacitinib

Applicant Name Pfizer, Inc

Approval Date, If Known November 6, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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?

5 years

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?

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#

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

YES
Explain:

! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! 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: *Philantha Bowen, MPH, RN*
Title: *Sr. Program Management Officer*
Date: *10/25/12*

Name of Office/Division Director signing form: *Badrul A. Chowdhury, MD, PhD*
Title: *Division Director*
Date: *10/26/12*

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/

PHILANTHA M BOWEN
11/06/2012

BADRUL A CHOWDHURY
11/07/2012

DEBARMENT CERTIFICATION
[FD&C Act 306(k)(1)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Nichie V. Kilgore
Signature of Company Representative

26 September 2011
Date



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: November 6, 2012

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 203214 (Xeljanz) - Labeling Request # 5

of Pages including cover: 36

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 203214
Tofacitinib Tablets
Pfizer

Dr. Kilgore:

Your labeling submission dated November 5, 2012, to NDA 203214 is currently under review. The enclosed label contains FDA revisions that are highlighted for identification purposes only. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert and medication guide on November 6, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
Medication Guide

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

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

/s/

PHILANTHA M BOWEN
11/06/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203214/ <u>Original 1</u> BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Xeljanz Established/Proper Name: tofacitinib Dosage Form: tablets, 5mg		Applicant: Pfizer Agent for Applicant (if applicable):
RPM: Philantha M. Bowen		Division: DPARP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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>Provide a brief explanation of how this product is different from the listed drug.</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 type="checkbox"/> This application relies on (explain)</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 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		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>November 21, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<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 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 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 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 type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<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 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
<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 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>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	November 6, 2012
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>)	Action(s) and date(s) AP: November 6, 2012
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. 	November 6, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 21, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

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 checked="" 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. 	November 6, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 21, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<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 	8/14/12
<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. 	Letters: 1/23/12; 4/17/12; 5/21/12; 7/24/12 Reviews: 1/20/12; 4/5/12; 5/1/12; 5/21/12; 10/11/12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 12/2/11 <input checked="" type="checkbox"/> DMEPA 6/11/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 9/27/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 10/2/12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews CMC 8/2/12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	12/19/11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<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 <u>July 11, 2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

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

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	11/1/11; 12/19/11; 1/26/12; 1/27/12; 2/27/12; 3/16/12; 3/26/12 (2); 4/5/12; 4/17/12; 5/15/12; 5/16/12; 5/22/12; 5/23/12; 6/4/12; 6/20/12; 6/26/12; 6/28/12; 7/9/12; 7/10/12; 7/19/12; 7/26/12; 7/31/12; 8/6/12; 8/7/12; 8/20/12; 10/5/12; 10/22/12; 10/26/12; 11/1/12 (2); 11/2/12 (2); 11/6/12
❖ Internal memoranda, telecons, etc.	1/5/12; 3/30/12; 11/6/12
❖ 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 type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 2/16/11
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 12/16/08 CMC-EOP2-3/7/11
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	5/9/12
• 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 11/6/12
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/6/12
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/20/12
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 3
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL review
• Clinical review(s) <i>(indicate date for each review)</i>	12/14/11; 6/26/12; 7/6/12; 9/26/12
• 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 type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	6/26/12; page 26
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None 6/20/12; 6/26/12 SEALD 10/22/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	10/21/11; 10/2/12; 10/29/12; 10/31/12; 11/5/12 11/6/2 <input type="checkbox"/> None 7/17/12; 10/24/12; 11/6/12
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 6/22/12 DSI letters: 8/31/12; 9/12/12; 10/2/12
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None <i>Concurrence on primary review</i>
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None <i>Concurrence on primary review</i>
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/14/11; 6/25/12; 10/1/12; 10/9/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None <i>Concurrence on primary review</i>
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/14/11; 6/25/12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/18/12
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/21/12; 7/27/12
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/5/11; 5/14/12; 7/3/12; 7/21/12; 9/21/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 7/9/12
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 3/8/12 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/3/12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None <i>Concurrence on primary review</i>
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/15/11; 6/19/12; 6/26/12; 7/24/12
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 3/9/12; 4/16/12; 5/22/12
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/26/12
<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) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 8/16/12 <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) (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 checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input 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/

PHILANTHA M BOWEN
11/06/2012

Bowen, Philantha

From: Kilgore, Nickie [Nickie.Kilgore@pfizer.com]
Sent: Tuesday, November 06, 2012 9:22 AM
To: Bowen, Philantha
Subject: RE: NDA 203214 - FDA Request #5 for Labeling Revisions
Importance: High

Hi Philantha,

This email is to confirm that Pfizer accepts all of the FDA recommendations for the PI and MG, as communicated in the attachment below. Thank you for your support in facilitating these communications.

Also, do you anticipate any other communications today?

Best regards,

Nickie

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Tuesday, November 06, 2012 8:23 AM
To: Kilgore, Nickie
Subject: NDA 203214 - FDA Request #5 for Labeling Revisions
Importance: High

Hello Nickie,

Attached is a label IR for your review (PI and MG). We are requesting a response today. Following your internal review if you are in agreement with our recommendations, you may provide a statement indicating your agreement to our revisions via email.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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/s/

PHILANTHA M BOWEN
11/06/2012



Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 2, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466
Subject: NDA 203214 – REMS Recommendations/Information Request #3	
Total no. of pages including cover: 7	

Comments: Please Acknowledge Receipt: TIME SENSITIVE

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Dear Dr. Kilgore:

Your submissions dated October 29 and 31, 2012, to NDA 203214 is currently under review. Reference is made to the REMS information request dated November 1, 2012.

In this information request, we have the following additional recommendations for your proposed REMS. We request that you provide a response to this information request, as it is inclusive of the aforementioned request and contains additional revisions.

The FDA-proposed insertions are underlined and deletions are in strike-out. Submit a clean copy and a tracked-change version of the proposed REMS and all REMS supporting documents, incorporating the recommendations in the attached request by 10 AM Monday, November 5, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/11-2-12

Clearance: Jafari/11-2-12
Worthy/11-2-12
Yim/11-2-12

Finalized: Bowen/11-2-12

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PHILANTHA M BOWEN
11/02/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: November 2, 2012

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 203214 (Xeljanz) - Labeling Request #4

of Pages including cover: 37

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Thank you.

NDA 203214
Tofacitinib Tablets
Pfizer

Dr. Kilgore:

Your labeling submissions dated October 29 and November 2, 2012, to NDA 203214 are currently under review. The enclosed label contains clarification FDA comments and/or request as to some of the changes made in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert and medication guide by 10 AM, Monday, November 5, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
Medication Guide

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

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/s/

PHILANTHA M BOWEN
11/02/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: November 1, 2012

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 203214 (Xeljanz) - Labeling Request #3 (Medication Guide)

of Pages including cover: 9

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Thank you.

NDA 203214
Tofacitinib Tablets
Pfizer

Dear Dr. Kilgore:

Your labeling submission dated October 29, 2012, to NDA 203214 is currently under review. The enclosed medication guide contains clarification FDA comments and/or request as to some of the changes. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the medication guide incorporating the recommendations in the attached medication guide by Friday, November 2, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Medication Guide

NDA 203214
Tofacitinib Tablets
Pfizer

Drafted: Bowen/10-31-12

Clearance: Jafari/10-31-12
Williams/10-31-12
Hulett/10-31-12

Finalized: Bowen/10-31-12

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PHILANTHA M BOWEN
11/01/2012



Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: November 1, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – REMS Recommendations/Information Request #2

Total no. of pages including cover: 4

Comments: **Please Acknowledge Receipt**

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Dear Dr. Kilgore:

Your submissions dated October 29 and 31, 2012, to NDA 203214 is currently under review. We have the following recommendations that will be required for your REMS assessments.

Include this information in the REMS Supporting Document.

REMS ASSESSMENT

1. A survey of the patients' knowledge and understanding of the serious risks of tofacitinib.
2. A survey of the prescribers' knowledge and understanding of the serious risks of tofacitinib.
3. A survey of the pharmacists' knowledge and understanding of the serious risks of tofacitinib.
4. An assessment and conclusions regarding the success of the REMS in meeting the stated goal.
5. An assessment of the communication plan including:
 - a. The date of launch of the communication plan (DHCPL, Dear Pharmacist Letter, website, and communication to professional societies)
 - b. The number of recipients of the DCHP letter
 - c. Date(s) of distribution of the DHCP letter
 - d. A copy of all documents included in each distribution
 - e. The professional meetings attended and professional societies that you communicated with
 - f. Information that the professional societies disseminated to their members and the timing of the dissemination.

NDA 203214
Tofacitinib
Pfizer, Inc.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/11-1-12

Clearance: Jafari/11-1-12

Finalized: Bowen/11-1-12

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/s/

PHILANTHA M BOWEN
11/01/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: October 26, 2012

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 203214 (Xeljanz) - Labeling Request #2

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Thank you.

NDA 203214
Tofacitinib Tablets
Pfizer

Dr. Nickie Kilgore:

Your labeling submission dated October 16, 2012, to NDA 203214 is currently under review. The enclosed label contain clarification FDA comments and/or request as to some of the changes made in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached document by the close of business on Monday October 29, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 203214
Tofacitinib Tablets
Pfizer

Drafted: Bowen/10/26-12

Clearance: Jafari/ 10-26-12
Yim/10-26-12
Buenconsejo/10-26-12

Finalized: Jafari/10-26-12

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/s/

LADAN JAFARI
10/26/2012



Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – REMS Recommendations/Information Request

Total no. of pages including cover: 32

Comments: **TIME-SENSITIVE; Please Acknowledge Receipt**

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Dear Dr. Kilgore:

Your amendment dated October 2, 2012, to NDA 203214 is currently under review. We have the following comments and/or recommendations for your proposed REMS. The REMS Supporting Document must be consistent with all changes made to the REMS.

GOAL

The goals have been further revised to the following:

“The goal of the XELJANZ REMS is to inform healthcare providers and patients about the serious risks associated with XELJANZ treatment.”

COMMUNICATION PLAN

Revise the communication plan as follows:

1. The following risks have been identified as part of the REMS:
 - serious and other important infections
 - changes in laboratory parameters, such as decreases in neutrophil counts, increases in low density lipoprotein cholesterol (LDL-c), decreases in hemoglobin levels, and transaminase elevations
 - malignancies and other lymphoproliferative disorders.

The risk of gastrointestinal perforation is not required to be included in the REMS and can be addressed via labeling.

2. The prescriber specialties of [REDACTED] (b) (4) have been removed from the list of targeted prescribers. [REDACTED] (b) (4)

3. See the attached REMS document, Dear Healthcare Provider Letter, Dear Pharmacist Letter, and Professional Society Letters for track changes.

REMS ASSESSMENT

Add the following to the REMS Assessment Plan:

1. A survey of pharmacists' knowledge and understanding of the serious risks of tofacitinib.

GENERAL COMMENTS

Resubmission Requirements and Instructions Submit the revised proposed REMS with attached materials. Provide a track changes and a clean version of all revised materials and documents.

Format Request: Submit your proposed REMS and other materials in WORD format. This requested format allows for a more efficient review process and facilitates the web posting preparation to ensure 508 document compliance. We prefer that the entire REMS document and attached materials be in a single WORD document. If certain documents, such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

Submit an official response to the NDA by COB Monday, October 29, 2012.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/10-25-12
Clearance: Jafari/10-25-12
Nikolov/10-25-12
Seymour/10-25-12
Finalized: Bowen/10-26-12

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/s/

PHILANTHA M BOWEN
10/26/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 22, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – PREA PMR Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE; Please Acknowledge Receipt**

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Your submission dated October 16, 2012, to NDA 203214 is currently under review. Reference is made to the PREA post-marketing requirement (PMR) for tofacitinib. Based on your proposed pediatric study request submission dated October 31, 2011, to IND 70903, you proposed a multiple-dose PK study in Juvenile Idiopathic Arthritis patients, which would be necessary in order to identify the dosing scheme for the PREA PMR study in PJIA patients. Confirm your agreement to conduct the following study and provide the requested milestone timeline.

A multiple dose pharmacokinetic study in children from 2 to less than 18 years of age with Juvenile idiopathic arthritis (JIA)

PMR Schedule Milestones:

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

Submit an official response to the NDA by 10 AM Wednesday, October 24, 2012.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/10-22-12

Clearance: Jafari/10-22-12
Seymour/10-22-12
Yim/10-22-12

Finalized: Bowen/10-22-12

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/s/

PHILANTHA M BOWEN
10/22/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

Memorandum of Facsimile Correspondence

Date: October 5, 2012

To: Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Company: Pfizer, Inc.

Fax: 860-686-7545

Phone: 860-441-5030

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products

Subject: NDA 203214 (Xeljanz) - Labeling Recommendation Request

of Pages including cover: 45

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Thank you.

NDA 203214
Tofacitinib Tablets
Pfizer

Dear Dr. Kilgore:

Your labeling submission dated August 13, 2012, to NDA 202314 is currently under review. The enclosed label contains clarification FDA comments and/or requests as for some of the changes made in the package insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these comments are not all-inclusive and we may have additional recommendations as we continue our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations in the attached package insert and medication guide by Friday, October 12, 2012, to the NDA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
Medication Guide

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/s/

PHILANTHA M BOWEN
10/05/2012



NDA 203214

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, DVM, Director
Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your October 21, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xeljanz (tofacitinib) tablets 5 mg and 10mg.

On August 10, 2012, we received your 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 November 21, 2012.

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 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 10, 2012.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, Ph.D., M.D.
Division Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
08/20/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 6, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – Carton/Container Labeling Information Request

Total no. of pages including cover: 5

Comments: **Please Acknowledge Receipt**

Document to be mailed: YES NO

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NDA 203214

Tofacitinib

Pfizer, Inc.

Dear Dr. Kilgore:

Your submission dated October 21, 2011, to NDA 203214, is currently under review and we have a request for labeling revisions. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Submit revised labeling incorporating the changes outlined below. Include a clean copy and a tracked change version of the package insert. Submit your response officially to the NDA and forward a courtesy copy to me via email.

We have the following recommendations/requests:

A. General Comment

1. Increase the prominence of the statement, 'Always Dispense with Medication Guide' by bolding and increasing the font size.

B. Container Labels

1. The established name includes the active ingredient and the finished dosage form. Relocate the dosage form, 'tablets', to appear after (Tofacitinib). For example:

Tradename
(Tofacitinib)
Tablets
10 mg

2. Relocate the 'Rx only' statement to the bottom of the principal display panel.

C. Container and Carton Labels

1. Revise the established name of the drug product to "tofacitinib tablets" while retaining the strength as 5 or 10 mg and include a footnote stating "each tablet contains 8 mg tofacitinib citrate equivalent to 5 mg tofacitinib, (b) (4)"

2. Submit revised bottle and carton label mock-ups that indicate the placement of the expiration date and lot number of the drug product (as per 21 CFR 201.1).

NDA 203214

Tofacitinib

Pfizer, Inc.

(b) (4)



E. Package Insert

1. Revise the DOSAGE FORMS AND STRENGTHS section of the package insert to include the information required by 21 CFR 201.57(c)(4)(ii), rather than referencing the DESCRIPTION section.
2. Revise the DESCRIPTION section so that it is clear that the strengths of the tablets, i.e., 5 and 10 mg, are in terms of the tofacitinib free-base. We recommend that you state the tofacitinib citrate equivalence in parentheses for added clarity.
3. Revise the molecular formula in the DESCRIPTION section to a standard format, i.e., with subscripts for numeric designations.
4. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the imprinting of the tablets as per 21 CFR 201.57(c)(17)(iii).
5. Revise the storage and handling statement to include the following reference “[see USP Controlled Room Temperature],” after the excursion temperature ranges.

(b) (4)



NDA 203214
Tofacitinib
Pfizer, Inc.

(b) (4)

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 203214
Tofacitinib
Pfizer, Inc.

Drafted: Bowen/8-2-12

Clearance: Jafari/8-3-12
Bertha/8-6-12
Peri/8-6-12

Finalized: Bowen/8-6-12

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/s/

PHILANTHA M BOWEN
08/06/2012

Bowen, Philantha

From: Greeley, George
Sent: Thursday, August 02, 2012 2:23 PM
To: Bowen, Philantha
Cc: Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Chowdhury, Badrul A
Subject: NDA 203-214 (b) (4)

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Philantha,

This email serves as confirmation of the review for (b) (4) (tofacitinib) which was conducted by the PeRC PREA Subcommittee on July 11, 2012.

The Division presented a partial waiver in patients birth to less than 2 years of age because this condition is rarely diagnosed in this age group. A deferral was also presented in pediatric patients 2-17 years of age for the treatment of rheumatoid arthritis.

The Division did not agree with the original pediatric plan submitted by the sponsor however, the issues were based on this being a brand new class of products. (b) (4) if approved, will be first oral drug approved for rheumatoid arthritis in over 10 years. Under PREA, the Division would require studies for Polyarticular JIA (b) (4) Study 3 will not be a PREA requirement for this product. The number of patients proposed by the sponsor is standard and is based on the numbers required in previous pediatric study trials.

The PeRC agreed with the Division to grant a partial waiver in patients birth to 23 months because studies would be impossible or highly impractical because JIA is not diagnosed in children below 2 years and to a deferral in patients 2-17 years because the product is ready for approval in adults.

The amended pediatric record is attached for (b) (4)



1_Pediatric_Record
.pdf (61 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025

Email: george.greeley@fda.hhs.gov

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 31, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib
Request for revisions to proposed REMS

Total no. of pages including cover: 5

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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Your NDA 203214 for tofacitinib is currently under review, and we have the following comments.

Your proposed REMS requires the following revisions:

5.1 Goals

Revise the goals of the REMS to be more consistent with current REMS goals and to leave open the potential to edit safety issues as necessary.

The goals of the tofacitinib REMS are:

- To inform healthcare providers about the serious risks associated with tofacitinib, (b) (4)
- To inform patients about the serious risks associated with tofacitinib treatment.

5.2 Medication Guide

Comments pertaining to the Medication Guide will be provided under separate cover.

5.3 Communication Plan

Revise the communication plan as follows:

General

1. Broaden the audience to include the following practitioners:

- (b) (4)
- Primary care providers and Emergency care physicians who may treat infections, including serious, opportunistic, and tuberculosis.

Dear Healthcare Provider Letter and Dear Pharmacist Letter

2. Submit the Dear Healthcare Provider and Dear Pharmacist Letters to the Agency to review.
3. Provide a detailed description of the method(s) that information about the known and potential risks associated with tofacitinib will be disseminated to practitioners. For example; for the journal ad, define which journals will be targeted.
4. Provide a detailed description of the method(s) you propose to utilize to capture relevant prescribers for implementation of the communication plan. For example, will you use professional organizations or a third-party contact database of the HCPs for which the mailing list will be derived?
5. Describe how you will identify pharmacists and/or pharmacies.

REMS Website

6. Add a REMS website, tofacitinibrems.com, to the elements of the communication plan.
 - a. We recommend that you include a prominent link on the product website's homepage for REMS materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."
 - b. In order to reach as many healthcare providers as possible, we suggest disseminating the DHCP letter through various media. For example, in addition to hardcopy, the letter could be sent electronically and be available on the product REMS website. If you do not choose to use electronic mailings, please provide a rationale for this decision.
7. The landing page of the separate REMS link should contain background information on the REMS along with the REMS communication materials.
 - a. We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks. In order for Pfizer to communicate certain risks about Tofacitinib, the Sponsor has worked with the FDA to develop materials to communicate the risks of [list risks; bullet format if multiple].
8. The REMS-related webpage(s) should not be a means to promote tofacitinib or any other Pfizer product.
9. Submit for review the web screenshot(s) for the REMS.
10. The Agency requires that the REMS website be independent of links to the promotional and/ or commercial website and non-REMS materials about the product. Do not include a link from the REMS website page back to the www.tofacitinib.com website.
11. Please note, the tofacitinib REMS webpage should also be accessible directly through a search engine.

5.4 General Comments

Resubmission Requirements and Instructions: Submit the revised proposed REMS with attached materials. Provide a track changes and a clean version of all revised materials and documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

Submit your response to the NDA no later than August 10, 2012. If you have any questions, please contact Philantha M. Bowen at 301-796-2466.

Drafted by: KWorthy/ July 17, 2012
cchung/ July 17, 2012

Initialed by: LJafari/ July 18, 2012
NNikolov/ July 31, 2012
SSeymour/ July 30, 2012

Finalized: cchung/ July 31, 2012

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/s/

CHRISTINE H CHUNG
07/31/2012

Bowen, Philantha

From: Kilgore, Nickie [Nickie.Kilgore@pfizer.com]
Sent: Thursday, July 26, 2012 9:49 AM
To: Bowen, Philantha
Subject: RE: Tofacitinib (NDA 203214): Clarification of PMR dated July 19th

Thanks so much, Philantha

From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Thursday, July 26, 2012 9:47 AM
To: Kilgore, Nickie
Subject: RE: Tofacitinib (NDA 203214): Clarification of PMR dated July 19th

Hi Nickie,

We have re-assessed the male fertility study submitted in the original NDA and have concluded that the study is a valid assessment and no further evaluation is necessary. Therefore, you may disregard the PMR request for this specific study outlined in our information request dated July 19, 2012.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
☎ 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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From: Kilgore, Nickie [mailto:Nickie.Kilgore@pfizer.com]
Sent: Wednesday, July 25, 2012 10:55 AM
To: Bowen, Philantha
Cc: Chung, Christine

Subject: Tofacitinib (NDA 203214): Clarification of PMR dated July 19th

Hi Philantha,

Welcome back! Hope things are going smoothly with the transition.

We have a question with regard to one of the items in the PMR of July 19th .

In the PMR, we received a request from the Division to conduct a nonclinical male fertility study. As we have previously conducted a male fertility study (Study 05GR051 Oral Fertility and Embryonic Development Study of CP-690,550-10 in Male and Female Rats, 2006), which was included in CTD Module 4.2.3.5.1, we would like a teleconference in order to better understand what further information is needed. Since the PMR requested a response by August 2nd, we would like to schedule a teleconference as soon as possible.

Thanks for your help,

Nickie

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/s/

PHILANTHA M BOWEN
07/26/2012



NDA 203214

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

ATTENTION: Nickie V. Kilgore, DVM
Director, Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) dated October 21, 2011, received October 21, 2011, submitted under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib Tablets, 5 mg and 10 mg.

We acknowledge receipt of your July 06, 2012, correspondence, received July 06, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of July 06, 2012.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Angela Ramsey at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/24/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 19, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib
Post marketing requirements

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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Your NDA 203214 for tofacitinib is currently under review.

We have identified the following post-marketing requirements (PMRs) for tofacitinib, provided that the application for tofacitinib gets approved. Please note that we may identify additional PMRs as we continue to review this application. Submit a correspondence with your agreement to conduct the PMRs, and provide the following milestones for each PMR: a) final protocol submission, b) study/trial completion date, and c) final report submission.

1. Nonclinical Male Fertility Study
2. Controlled clinical trial to evaluate the long term safety of tofacitinib in patients with rheumatoid arthritis. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy. Submit a draft proposal to address this PMR.
3. Assessment of pharmacokinetic parameters and dosing, efficacy, and safety of tofacitinib in the pediatric population ≥ 2 years to < 17 years with polyarticular JIA.

Submit your response to the NDA no later than August 2, 2012. If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: SSeymour/ July 13, 2012
cchung/ July 17, 2012

Initialed by: LJafari/ July 18, 2012
SYim for SSeymour/ July 19, 2012

Finalized: cchung/ July 19, 2012

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/s/

CHRISTINE H CHUNG
07/19/2012



Food and Drug Administration
Center for Drug Evaluation and Research
ODE II / DPARP / HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Memo to File

NDA: 203,214

SD #s: 0028, 0030, 0031

Reviewer: Nikolay P. Nikolov, M.D., CDER/OND/DPARP

Submitted: June 25, 2012

Reviewed: July 06, 2012

Product: Tofacitinib (CP-690,550), an inhibitor of Janus associated kinases (JAKs)

Proposed use: Treatment of rheumatoid arthritis (RA)

Sponsor: Pfizer

Submission: Type A Meeting package: Pfizer is requesting a Type A meeting to discuss and reach agreement on the safety analyses needed to support an assessment of the benefit-to-risk of tofacitinib and to support approval of the NDA during the first review cycle. Specifically, Pfizer proposes to discuss alternative strategies to respond to key elements of the 20 June Clinical Information Requests (IRs) in a more expeditious manner while still addressing the Agency's concerns.

Background Information:

After the Advisory Committee meeting on May 09, 2012, and after discussion among members of the clinical and statistics teams, several issues were identified as potential limitations with regard to the safety data presentation and analyses to better determine the safety profile of tofacitinib 5 mg and tofacitinib 10 mg. events of interest due to the complexity of the trial design (see , such as early escape options and unequal randomization. These issues included:

1. Data were analyzed for patients as randomized and not as treated. For example, patients who were on placebo and transition to active treatment at Months 3 or 6 were counted under the respective active treatment arm from that point on, instead of time "zero". Presenting the safety data for patients as treated may allow for a more precise assessment of crude proportions of patients with AEs for any given time period, even though this approach may not affect the incidence rates of AEs, adjusted for actual exposure to the drug.
2. From the submission, it was not clear whether the rules for capturing and reporting of AEs were applied consistently within the RA development program which may have introduced a bias in AE reporting. For example, a 30-day window from the last dose for capturing AE was applied only for deaths, and not other AEs.
3. Pooled safety analyses were presented for the five Phase 3 randomized controlled trials (A3921032, A3921044, A3921045, A3921046, and A3921064) and separately for the Phase 2

dose-ranging studies (A3921025, and A3921035). However, the two pivotal Phase 2 studies were of similar design and patient population to the Phase 3 studies and could be included in the pooled analyses to increase the overall sample size for assessment of controlled data.

4. Long-term extension study A3921041 included patients who completed Japanese Phase 2 studies which were not included in the pooled analyses of the controlled studies. Therefore, excluding these patients in the open label extension analyses may allow for more accurate comparison with the analyses from the controlled studies.

To address these points, the Sponsor was asked to provide additional analyses. The Division sent several information requests to the applicant requesting safety datasets with selected variables from existing database and additional analyses accounting for differences in length of exposure and the cross-over nature of the design. Teleconferences were held between the Division and the applicant to clarify some issues or roadblocks regarding the requests.

The Type A meeting requested by the Sponsor is to discuss the potential for alternative safety analyses to address the Agency's questions, and the potential impact of the submission timing on the review of the NDA, particularly in light of the August 21, 2012 action date.

Summary of Meeting Package:

1.1. Assignment of events to treatment and pooling strategy

- Assignment of AEs to treatment: The Sponsor clarifies that events occurring on tofacitinib, regardless of previous placebo or adalimumab treatment, are attributed to tofacitinib at the administered dose.
- Assignment of AEs for time period: The Sponsor clarifies that assignment of AEs to treatment used the time period on study and not on treatment as requested in the Information Request. Pfizer has the following concerns with this approach based on study design considerations, as:
 - The tofacitinib Phase 3 trials were not designed as crossover studies. Patients were advanced, from placebo to tofacitinib only, based on disease activity at different timepoints. Pooling of these groups is therefore confounded by period effect over the short term.

Reviewer's comment: *This is a valid argument as patients who escape from placebo to active treatment due to active disease represents a group of patients with more active disease who may be more prone to developing adverse events and therefore may represent a somewhat different population than the one originally randomized to active treatment with a different baseline risk.*

- Both patients and investigators were aware that only active drug was administered in the later portion of the clinical trials, making these time intervals essentially "open-label", further confounding the proposed pooling strategy.

Reviewer's comment: *The issue of open label is not as relevant for assessment of safety as it is for efficacy. It is unlikely that this would significantly affect the safety assessment of major events of interest. Further, the studies remain blinded and randomized to tofacitinib 5 mg and 10 mg BID.*

- Data collection frequency was significantly different for the different time intervals, introducing acquisition bias into the proposed strategy. For example, study 1046 had visits at baseline, 2 weeks, 1 month, 2 months, 3 months, 4.5 months, 6 months, 9 months and 12 months. Thus, during Months 0-3, there were 5 visits (at baseline, 2 weeks, 1, 2, and 3 months), whereas during Months 3-6 there were 3 visits (at 3 months, 4.5 months and 6 months), and during the 6-9 month period there were 2 visits (at 6 and 9 months).

Reviewer's comment: *This is a valid argument as the different intensity of assessments may introduce bias in the AE assessment for patients who escape/transition from placebo to active treatment and pooling this way not be the most appropriate approach.*

Based on these concerns, Pfizer proposes that the most appropriate tofacitinib to placebo comparison is between originally randomized dose groups in months 0-3.

Reviewer's comment: *This is not unreasonable. We agreed internally on the 0-3 month's period to be the cleanest comparison to placebo. In addition, Pfizer will need to pool also Phase 2 studies, stratify by study, and include sensitivity analyses for months 0-3 to include "as treated" patients who transitioned from placebo to active treatment by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064), but excluding patients who escaped due to active disease. These analyses however, will only allow for tofacitinib to placebo comparison, which is needed for labeling.*

To assess the safety profile of tofacitinib 5 mg relative to 10 mg BID, for the 0-6 and 0-12 month periods of the 7 studies, with respect to major events of interest, a different approach was discussed internally, where the pooled data would be stratified by study, and analyzed using Cox proportional hazard model of:

- *Only patients originally randomized to tofacitinib 5 and 10 mg BID*
- *Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064).*
- *Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.*

These analyses represents a more scientifically sound approach to account for the complex trial design and to allow for comparative safety assessment of tofacitinib 5 mg vs. 10 mg BID. These analyses will be required for the regulatory decision on the NDA and will be conducted by the FDA statistical review team. This approach will be presented to the Sponsor as detailed in the Comment to Sponsor section to allow for further discussion at the meeting.

- **Ascertainment of AEs:** The reporting windows for reporting of AEs are based on company-wide standard operating procedures:
 - For deaths: All deaths are reported as SAEs and in the NDA were reported for deaths that occurred at any time after treatment and separately for deaths that occurred within 30 days of last dose. Furthermore, investigators are required, per protocol, to report all deaths (and SAEs) through 28 days after the last administration of tofacitinib, enhancing the reliability of accurate reporting of these events
 - For SAEs: The reporting period begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.

Reviewer's comment: *If the window for reporting is 28 days after last administration, it is unclear how the Sponsor can ascertain that the death/SAE occurred within 30 days of last dose.*

- For AEs: Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit. For adverse events and/or clinically significant laboratory abnormalities, follow-up

by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. All treatment-emergent AEs that were reported to the study databases were included in the safety summaries, regardless of when the data were collected, up until database lock for the clinical study.

- For Laboratory tests: All laboratory data that was reported to the clinical database was included in the safety summaries, regardless of when the data were collected, until database lock for the clinical study

Reviewer's comment: *From this description, it is not clear whether the 30-day post treatment applies to non-serious AEs and laboratory data and warrants clarification.*

- Incidence Rates by 6-month Time Intervals:
 - Pfizer has previously submitted to the NDA the non-cumulative incidence of the following safety events of interest broken down by 6-month intervals: Serious infections, Herpes zoster, Malignancies, Lung cancer, Breast cancer, and NMSC.
 - Pfizer proposes to provide similar analyses for opportunistic infections, tuberculosis, and gastrointestinal perforations

Reviewer's comment: *This is acceptable.*

- Pfizer also proposes not to break down these periods to 3-month intervals.

Reviewer's comment: *This is acceptable, even though we have not specifically asked for this.*

1.2 Pfizer proposes not include the Phase 2 data in the pooled analyses with the justification that it represents only about 10% of the safety database and is unlikely to add substantially to the understanding of the benefit:risk assessment of tofacitinib.

Reviewer's comment: *Studies 1025 and 1035 however, are of sufficiently similar design and patient population to the Phase 3 studies and warrant inclusion in the integrated analyses.*

Comments to Sponsor:

1. Pfizer believes that the safety analyses agreed in the pre-NDA meeting and provided in the original submission are optimal for assessing the safety of tofacitinib. Based on our understanding of the Agency's current concerns, Pfizer proposes that supplementation of the NDA with alternative additional analyses will answer the key elements of the questions posed by the Agency in its 4 June IR (modified 20 June). Does FDA concur?

FDA Response:

We acknowledge your methodological considerations, but we do not agree with your proposal. One difference is the studies for inclusion in the safety analysis. Studies 1025 and 1035 are of sufficiently similar design and patient population to the Phase 3 studies. Therefore, we request that they are included in the integrated safety analyses. (b) (4)

For transparency, we provided the following information on analyses we plan to conduct with the safety data.

1. To assess the safety profile of tofacitinib 5 mg BID relative to 10 mg BID for the 0-6 and 0-12 month periods of the 7 studies, with respect to events of interest (listed in Question 1.4), stratified by study, using Cox proportional hazard model of:
 - a) Only patients originally randomized to tofacitinib 5 and 10 mg BID
 - b) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064).
 - c) Patients originally randomized to tofacitinib 5 and 10 mg BID + patients who transitioned to tofacitinib 5 and 10 mg BID by study design (month 3 for studies 1032 and 1045, and Month 6 for studies 1044, 1046, and 1064) + patients who escaped to tofacitinib 5 and 10 mg BID due to active disease.
2. We plan on comparing the safety profile of tofacitinib, relative to adalimumab, with respect to events of interest (listed in Question 1.4) using data from studies 1035 and 1064, separately.

1.1. Assignment of events to treatments and pooling strategy:

FDA Response:

We agree that the least confounded tofacitinib to placebo comparison is between "originally randomized" dose groups in months 0-3. Summary statistics (counts and %) should be presented pooled to include all 7 studies. All statistical tests for events of interest (listed in Question 1.4) should be stratified by study. In addition, sensitivity analyses should be conducted, for months 0-3 including patients who transitioned from placebo to active treatment by study design (month 3 for studies 1032 and 1045) in months 3 to 6.

Your proposal to provide Kaplan-Meier plots by randomized sequence over 0-12 months for the 7 studies is acceptable.

From the description of reporting windows (Appendix 1 in the briefing package) several points need clarification:

- If the window for reporting of death and SAE is 28 days after last dose administration,

- how can you ascertain that the event occurred within 30 days of last dose?**
- **It is not clear whether the 30-day post treatment window applies to non-serious AEs and laboratory tests.**

1.2. Studies for inclusion in the safety analyses

FDA Response:

Refer to the Comments to Question 1 above.

1.3. Time periods and windows

FDA Response:

Refer to the Comments to Question 1.1 above.

1.4. Events for analysis

FDA Response:

Your proposal to include the following events in the requested analyses: death, lymphoma, solid organ tumor (malignancies), opportunistic infection, tuberculosis, serious infections, herpes zoster, and CV MACE events is acceptable.

2. Could the Agency provide insight into how the projected timelines for responding to the June information requests could impact the review of the NDA? For example, as long as the totality of the data support product safety and efficacy, could some of the desired analyses be performed as a post-approval commitment and be submitted to the agency as a labeling supplement after initial NDA approval?

Pfizer's response (to June 4th and June 20th IRs) could not be provided to the Agency prior to September 2012, approximately 1 month after the PDUFA Action date. What would the implications be on the review of the NDA?

Following the teleconference on 19 June and the Clinical IR received on 20 June, Pfizer has considered the key components of the request and has made a proposal which Pfizer believes will address the intent of the 4 June and 20 June IRs. This proposal would result in submission of additional data by end of July 2012. If this proposal is reasonable and suitable to support an approval decision, would this timing permit completion of the review within the current PDUFA timeline, with any additional data provided post-approval?

FDA Response:

As a clarification, the June 20th IR supersedes the June 4th IR. The June 20th Clinical IR is focused on the information required for regulatory decision making. Therefore, the required analyses should be submitted as soon as possible to allow for a determination of a regulatory action on the application by the PDUFA goal, August 21, 2012.

Appendix 1. Key Design Features of NDA 203,214 Phase 2 and 3 Randomized Controlled Studies for Efficacy and Safety

Key Design Features of the Phase 3 Studies in RA for Efficacy and Safety						
Protocol	Patient Population	Design Duration	Enrolled Randomization	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
Patients with incomplete response to prior TNF inhibitor						
A3921032	Moderate-to-severe RA TNF-IR, Stable background MTX	R, DB, PC Phase 3 6 months	399 2:2:1:1	CP 5 mg BID + MTX CP 10 mg BID + MTX Placebo (→CP 5 mg BID @ Mo3)+ MTX Placebo (→CP 10 mg BID @ Mo3)+ MTX	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
Patients with incomplete response to MTX or other DMARDs						
A3921044	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 3 Two years*	797 4:4:1:1	CP 5 mg BID + MTX CP 10 mg BID + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR)+ MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR)+ MTX	ACR20 mTSS HAQ-DI DAS28<2.6	Month 6 Month 6 Month 3 Month 6
A3921045	Moderate-to-severe RA DMARD-IR, No background to Month 3	R, DB, PC Phase 3 6 months	610 4:4:1:1	CP 5 mg BID CP 10 mg BID PBO → CP 5 mg BID @ Mo 3 PBO → CP 10 mg BID @ Mo 3	ACR20 HAQ-DI DAS28<2.6	Month 3 Month 3 Month 3
A3921046	Moderate-to-severe RA DMARD-IR, Stable background DMARDs [#]	R, DB, PC Phase 3 One-year	792 4:4:1:1	CP 5 mg BID + DMARD CP 10 mg BID + DMARD PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR) + DMARD PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR) + DMARD	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6
A3921064	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, AC Phase 3 One year	717 4:4:1:1:4	CP 5 mg BID + PBO SC+ MTX CP 10 mg BID + PBO SC + MTX PBO (→CP 5 mg BID @ Mo 6 or Mo3 if NR) + PBO SC + MTX PBO (→CP 10 mg BID @ Mo 6 or Mo3 if NR) + PBO SC + MTX PBO + Adalimumab + MTX	ACR20 HAQ-DI DAS28<2.6	Month 6 Month 3 Month 6 Month 6
Key Design Features of the Pivotal Phase 2 Studies in RA for Efficacy and Safety						
Protocol	Patient Population	Design Duration	Enrolled Randomization	Treatment Arms (transition and escape for NR)	Primary Endpoints	Timepoint
A3921025	Moderate-to-severe RA MTX-IR, Stable background MTX	R, DB, PC Phase 2, Dose- ranging 6 months	507 1:1:1:1:1:1	CP 1 mg BID (→CP 5 mg BID @ Mo3 if NR)+ MTX CP 3 mg BID (→CP 5 mg BID @ Mo3 if NR)+ MTX CP 5 mg BID + MTX CP 10 mg BID + MTX CP 15 mg BID + MTX CP 20 mg OD (→CP 5 mg BID @ Mo3 if NR)+ MTX Placebo (→CP 5 mg BID @ Mo3 if NR)+ MTX	ACR20	Month 3
A3921035	Moderate-to-severe RA DMARD-IR, No background therapy	R, DB, AC Phase 2, Dose- ranging 6 months	384 1:1:1:1:1:1	CP 1 mg BID (→CP 5 mg BID @ Mo3 if NR) CP 3 mg BID (→CP 5 mg BID @ Mo3 if NR) CP 5 mg BID CP 10 mg BID CP 15 mg BID Adalimumab (→CP 5 mg BID @ Mo3) Placebo (→CP 5 mg BID @ Mo3 if NR)	ACR20	Month 3

Source: Summary of Clinical Efficacy, Clinical Study Reports for studies A3921032, A3921044, A3921045, A3921046, A3921064

*-One year efficacy data submitted for Study A3921044; [#]-Background DMARD therapy in Study A3921046: 84% of subjects on MTX, ~1/2 on combination DMARDs; AC-active control (adalimumab, study A3921064); BID-two times daily; DMARDs-disease-modifying anti-rheumatic drugs; IR-incomplete response; MTX-methotrexate; mTSS-modified total Sharp Score; NR-non-responder defined as patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender joint counts over baseline at Month 3 visit; PBO-placebo; PC-placebo (add-on for studies A3921032, A3921044, A3921046, A3921064)-controlled; SC-subcutaneous; TNF-tumor necrosis factor. CP=CP-690.550/tofacitinib

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/s/

NIKOLAY P NIKOLOV
07/06/2012

SARAH K YIM
07/06/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 28, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib
Additional information regarding AER 2011193470

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Response requested by July 16, 2012

Document to be mailed: YES NO

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Your NDA 203214 for tofacitinib is currently under review, and we have the following request for information.

Internal review of AER 2011193470 Serious Adverse Event Case (Patient 1024-15081007), concluded that this is a likely case of drug-induced liver injury which meets Hy's Law criteria. Of particular concern is the temporal relationship to the addition of tofacitinib, and the lack of autoimmune serologies to corroborate a diagnosis of autoimmune hepatitis. Provide an update on the case with any follow up information, clinical course and laboratory data.

Submit the requested information as an official response to the NDA no later than July 16, 2012. If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: NNikolov, SYim/ June 28, 2012
cchung/ June 28, 2012

Initialed by: LJafari/ June 28, 2012

Finalized: cchung/ June 28, 2012

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/s/

CHRISTINE H CHUNG
06/28/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 20, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib
This communication prioritizes the information requested in our 6/4/12
correspondence

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Document to be mailed: YES NO

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Your NDA 203214 for tofacitinib is currently under review. This communication is intended to clarify and prioritize the information requested in our 6/4/12 correspondence.

Seven trials to include in integrated analysis

- Five phase 3 and two phase 2 trials – 1025, 1035, 1032, 1046, 1044, 1045, 1064

Timing of Events

- Events within 30 days of stopping treatment or decreasing dose. No 30 day window (hard stop) for placebo to tofacitinib cross over, increasing tofacitinib dose.

Time Intervals

- 0-3 months
- 0-6 months
- 0-12 months

Events of interest

- death
- lymphoma
- solid organ tumor
- opportunistic infection
- TB
- SAE infection
- herpes zoster
- CV MACE events

Provide tables for the above time intervals for each event of interest and also provide KM curves for 0-12 months.

Events of interest for labeling

- Hemoglobin
- Lipids
- Neutrophils
- LFTs
- Common AEs

These events can be for 0-3 month time interval as long as laboratory changes have reached a plateau.

Submit the requested information and datasets as an official response to the NDA. If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: NNikolov, SYim, SSeymour, BChowdhury, JBuenconsejo/ June 20, 2012
cchung/ June 20, 2012

Initialed by: LJafari/ June 20, 2012

Finalized: cchung/ June 20, 2012

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/s/

CHRISTINE H CHUNG
06/20/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 4, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib- Request for information
Format of data for Safety analyses

Total no. of pages including cover: 10

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by agreed on timelines

Document to be mailed: YES NO

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are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-3420. Thank you.**

Your NDA 203214 for tofacitinib is currently under review, and we have following requests for information:

- A. In our Information Request correspondence dated May 22, 2012, we requested that you submit three separate datasets for each of the safety endpoints (death, malignancy, and serious infections). We specifically asked for the following datasets:
1. death (within 30 days of last dose)
 2. malignancy (solid tumor, hematologic)
 3. serious infections, including opportunistic infection and tuberculosis.

While the structure of the datasets remains, we would like to ask that you include the following additional events of interest into the datasets:

1. non-melanoma skin cancer (under malignancy)
2. herpes zoster (under serious infection)
3. cardiovascular events (fourth datasets called “other events”)
4. gastrointestinal perforations (fourth datasets called “other events”)
5. interstitial lung disease (fourth datasets called “other events”)

In summary, the four datasets will have the following events of interest:

1. Death (all deaths within 30 days of last dose)
2. Malignancy (all types, solid tissue malignancy, lung cancer, breast cancer, lymphoma, non-melanoma skin cancer)
3. Infections including serious (all infections, pneumonia, opportunistic infection, tuberculosis, and herpes zoster) and all infections (pneumonia and herpes zoster)
4. Other events (including cardiovascular events, GI perforations, and interstitial lung disease [flagged])

In addition, in the “death” dataset, include a variable for cause of death. Also, all four datasets should include all randomized patients from Studies 1025, 1035, 1032, 1045, 1044, 1046 and 1064.

Submit all these information and datasets on or before **June 22, 2012**.

- B. Information Request conveyed in May 31, 2012, teleconference.

Data sets:

1. Phase 2 studies (Study 1025 and Study 1035) only data on patients on placebo, adalimumab, tofacitinib 5 mg and 10 mg BID, and data on patients who switched to 5 mg BID
2. All 5 phase 3 studies [Studies 1045, 1032, 1044, 1046, 1064]

Timing of events:

1. For the 7 trials of interest described below, provide a brief summary of your collection, reporting, and analyses of adverse events for each treatment group in your NDA, with a specific focus on collection and handling of events after treatment ends. Your summary should address and provide justification for the reporting windows for deaths, SAEs, AEs, lab values used in the safety analyses for each treatment group in your NDA.
2. Based upon our teleconference on May 31, 2012, it appears that your safety analyses may utilize a different window for analyses of adverse events after treatment ends and for different types of events. Therefore, we request the analyses described below with the following two different methods for handling of adverse event windows.
 - a. Events reported on treatment only
 - b. Events reported within 30 days of stopping treatment. In cases where patients have crossed over from placebo to tofacitinib, this 30 day window would not exist as events that occur on tofacitinib should be counted as a tofacitinib event.

Events of Interest:

1. All cause death
2. Death from events of interest
 - a. all malignancy
 - b. solid tissue malignancy
 - c. lung cancer
 - d. breast cancer
 - e. infection
 - f. pneumonia
 - g. opportunistic infection
 - h. cardiovascular events
 - i. interstitial lung disease
3. Serious Adverse Events (SAE)
 - a. all malignancy
 - b. solid tissue malignancy
 - c. lung cancer
 - d. breast cancer
 - e. lymphoma
 - f. non-melanoma skin cancer
 - g. all infection
 - h. pneumonia
 - i. opportunistic infection
 - j. tuberculosis
 - k. herpes zoster
 - l. cardiovascular events
 - m. gastrointestinal perforation
 - n. interstitial lung disease

4. Adverse events of interest (some of these may be captured as SAEs also)
 - a. non-melanoma skin cancer
 - b. all infection
 - c. pneumonia
 - d. tuberculosis
 - e. herpes zoster
 - f. cardiovascular events
 - g. gastrointestinal perforation
 - h. interstitial lung disease
5. Common adverse events for labeling

Other areas of interest:

Laboratory values (blood cell type count, lipid levels, liver enzymes, creatinine, etc) may need to be analyzed using the above criteria.

Time Intervals:

1. 0 to 3 months
2. 3 to 6 months
3. 6 to 9 months
4. 9 to 12 months
5. 12 to 15 months (if data available)
6. 0 to 6 months
7. 0 to 12 months
8. 12 months and beyond

Analyses:

1. Produce Kaplan-Meier plots by treatment group with a table showing number of patients with at least one event over number at risk
2. Rates by time period (number of patients with at least one event over patient-year exposure), see sample Tables below.

FOR ALL SUMMARIES/ANALYSES: Placebo patients who escaped or crossed over to CP should be counted in the denominator in both groups based on their on-treatment time. The numerator count will depend on the timing of event (see above).

Hypothetical examples:

1. In a 12 month study, patient A was in placebo for first 3 months, and escaped to CP 5 mg at month 3, and diagnosed with malignancy at month 5. Patient A will be double counted in the denominator at the 0 to 3 months interval, with 0 event in the placebo numerator, and 1 malignancy event in the CP 5 mg numerator with exposure time being month 2. Furthermore, patient A should be counted in the placebo denominator at the following time intervals: 0 to 3 months, 0 to 6 months, and 0 to 12 months. Patient A should also be counted in the CP 5 mg denominator at the following time intervals: 0 to 3 months, 3

to 6 months (if applicable), 6 to 9 months (if applicable), 0 to 6 months and 0 to 12 months.

2. In a 12 month study, patient B was in placebo for the first 6 months, and switched over to CP 10 mg at month 6. Patient B should be counted in the placebo denominator at the following time intervals: 0 to 3 months, 3 to 6 months, 0 to 6 months, and 0 to 12 months. Patient B should also be counted in the CP 10 mg denominator at the following time intervals: 0 to 3 months, 3 to 6 months (if applicable), 0 to 6 months, and 0 to 12 months.

Datasets to be analyzed and Tables to be produced:

1. Events of Interest # 1 (death), #2 (death by events listed above), and #3 (SAEs by events listed above)
 - a. Studies 1025, 1035, 1032, 1046, 1044, 1045, 1064, individually
 - b. Pooled: All Phase 2 and 3 studies (1025, 1035, 1032, 1046, 1044, 1045, 1064)
 - c. Pooled MTX/DMARD background: Studies 1025, 1032, 1046, 1064, 1044
 - d. Pooled Monotherapy: Studies 1035, 1045

Sample Tables to consider:

Period: 0 to 3 months				
	CP 5 mg†	CP10 mg†	Placebo	Adalimumab*
Total no. of patients				
Total no. of events (if applicable)				
No. of patients with at least one event				
Pt-year exposure				
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)				

† Includes patients who escaped at Month 3 or crossed over at Month 6 and begin CP treatment

* Study 1064 only

Period: > 3 to 6 months				
	CP 5 mg†	CP10 mg†	Placebo‡	Adalimumab
Total no. of patients				
Total no. of events (if applicable)				
No. of patients with at least one event				
Pt-year exposure				
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)				

† Includes patients who escaped at Month 3 or crossed over at Month 6 and begin CP treatment

‡ Includes patients who stayed on placebo after Month 3

* Study 1064 only

Period: > 6 to 9 months				
	CP 5 mg†	CP10 mg†	Placebo‡	Adalimumab
Total no. of patients				
Total no. of events (if applicable)				
No. of patients with at least one event				
Pt-year exposure				
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)				

† Includes patients who escaped at Month 3 or crossed over at Month 6 and begin CP treatment

‡ Includes patients who stayed on placebo after Month 3 (may be 0)

* Study 1064 only

Period: > 9 to 12 months			
	CP 5 mg†	CP10 mg†	Adalimumab
Total no. of patients			
Total no. of events (if applicable)			
No. of patients with at least one event			
Pt-year exposure			
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)			

† Includes patients who escaped at Month 3 or cross-over at Month 6 and begin CP treatment

* Study 1064 only

Period: 0 to 6 months				
	CP 5 mg [†]	CP10 mg [†]	Placebo [‡]	Adalimumab*
Total no. of patients				
Total no. of events (if applicable)				
No. of patients with at least one event				
Pt-year exposure				
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)				

[†] Includes patients who escaped at Month 3 or crossed over at Month 6 and begin CP treatment

[‡] Includes all placebo patients (who stayed or escaped)

* Study 1064 only

Period: 0 to 12 months				
	CP 5 mg [†]	CP10 mg [†]	Placebo [‡]	Adalimumab*
Total no. of patients				
Total no. of events (if applicable)				
No. of patients with at least one event				
Pt-year exposure				
Incidence rate, in no. of patients with at least one events/pt-year (95% confidence interval)				

[†] Includes patients who escaped at Month 3 or cross-over at Month 6 and begin CP treatment

[‡] Includes all placebo patients (who stayed or escaped)

* Study 1064 only

2. Events of Interest # 4 (AE of interest) and #5 (Common AEs)
 - a. Pooled: All Phase 2 and 3 studies

Provide the same Tables you have in the Integrated Summary of Safety by 0 to 3 months, 3 to 6 months, 0 to 6 months, and/or 0 to 12 months, if applicable.

FOR ALL SUMMARIES: Placebo patients who escaped or crossed over to CP should be counted in the denominator in both groups based on their on-treatment time. The numerator count will depend on the timing of event (see above).

For example, Table 75 of the ISS includes the AE leading to discontinuation from study for Phase 3 studies with Background DMARDs (up to 3 Months) and Table 76 includes the AEs from 3 to 6 months. The numerator and denominator for the CP dose groups from 0 to 3 months should include those patients who escaped to CP at Month 3 or cross-over at Month 6 since these patients who switched were also treated with CP. Similarly, the numerator and denominator for the CP dose groups from 3 to 6 months should also be adjusted to account for the switches.

Submit the requested information and datasets as an official response to the NDA by the agreed upon timelines or provide timelines for when the information will be submitted.

If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: JBuenconsejo, YMKim, MSoukup, NNikolov, SYim, SSeymour/ June 1, 2012
cchung/ June 1, 2012

Initialed by: LJafari/ June 4, 2012

Finalized: cchung/ June 4, 2012

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/s/

CHRISTINE H CHUNG
06/04/2012



NDA 203214

INFORMATION REQUEST

Pfizer Inc.
Attention: Nickie V. Kilgore, DVM
Director, Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Kilgore:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tofacitinib tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response by April 15th 2012 in order to continue our evaluation of your NDA.

1. The Agency is still developing its regulatory standards for using QbD approaches to analytical methods. Therefore, the proposed (b) (4) has not been assessed and no regulatory action will be taken.

(b) (4)

b. The system suitability tests were performed at the target conditions, as indicated in

(b) (4)



(b) (4)



(b) (4)



1 Page has been Withheld in Full as b4 (CCI/
TS) immediately following this page

(b) (4)

4. The revised acceptance criterion for total impurities is still not supported by the actual batch data and needs to be (b) (4)
5. Your proposed acceptance criterion of (b) (4) for the disintegration test is not supported by any data and is not acceptable. Based on the information you provided, the disintegration time is (b) (4) for all the (b) (4) studies and even for the studies on the (b) (4) tablets. Therefore, an acceptance criterion of less than (b) (4) should be implemented for the disintegration test of your product. Provide the revised specifications table for your drug product and update your application accordingly. However, if you do not agree with our recommendation, justify your proposal with adequate supportive data.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
06/01/2012
Signed for Eric Duffy



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 23, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib- Request for information
AE Incidence separate analyses

Total no. of pages including cover: 3

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by Thursday, May 31, 2012

Document to be mailed: YES NO

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Your NDA 203214 for tofacitinib is currently under review, and we have following request for information:

Provide separate analyses for 5 and 10 mg BID dosing for the non-cumulative incidence over time for the following events of interest, pooled from all Phase 2, Phase 3 and LTE studies in RA (as of September 29, 2011, the 120-day safety update data cut-off):

1. Malignancy, excluding non-melanoma skin cancer
2. Lymphoma
3. Lung cancer
4. Breast cancer
5. Non-melanoma skin cancer
6. Serious infections
7. Opportunistic infections
8. Tuberculosis

Please use the following format for each outcome:

CP 5 mg BID	Overall	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months	>36 months
Total number of patients								
Total patients with ≥ 1 event, n (%)								
Exposure for event, patient-years								
Incidence rate, per 100 patient-years (95% CI)								

CP 10 mg BID	Overall	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months	>36 months
Total number of patients								
Total patients with ≥ 1 event, n (%)								
Exposure for event, patient-years								
Incidence rate, per 100 patient-years (95% CI)								

Submit the requested information as an official response to the NDA by Thursday, May 31, 2012, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: NNikolov, SYim, JBuenconsejo, YMKim/ May 22, 2012
cchung/ May 22, 2012

Initialed by: LJafari/ May 23, 2012

Finalized: chung/ May 23, 2012

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/s/

CHRISTINE H CHUNG
05/23/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 22, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib- Request for information
Safety analyses- statistics

Total no. of pages including cover: 4

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by Tuesday, May 29, 2012

Document to be mailed: YES NO

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notify us immediately by telephone at (301) 796-3420. Thank you.**

Your NDA 203214 for tofacitinib is currently under review, and we have following request for information:

As we mentioned during our brief teleconference with you on May 16, 2012, we will be conducting additional safety analyses of the data. Specifically, we will be evaluating key safety endpoints including death (within 30 days of last dose), malignancy (solid tumor, hematologic), and serious infections, including opportunistic infection and tuberculosis.

Sent by email with this correspondence is a spreadsheet that contains a listing of subjects who experienced malignancy, opportunistic infections, or death. Please review and update the spreadsheet if we missed any subjects in each of these categories. For the long-term extension, provide the index study-subject ID (i.e., the original study these subjects were on and their ID numbers) for cross-referencing. Clarify whether the day of death and the last day on treatment (extracted from Integrated Summary of Safety and 120-Day Safety Update listings and narratives) for the long-term extension included the time the subjects were on the original study, or were these based only during the long-term extension portion. For example, under the tab DEATH, the day of death and the last day of treatment for subject-ID 1024-11221065 (LTE CP10 mg BID) were 1. Was this subject a placebo in the original study and exposed for a day of CP10 mg in the LTE study? If not, provide the total exposure for each of these subjects (for malignancy, death, and opportunistic infections) from the time they were on treatment.

Furthermore, provide a new TAB with subject-level listing of subjects who had serious infections (n=206) broken down by dose.

In order to expedite our review, submit a separate dataset for each of the safety endpoints (death, malignancy, and serious infection). In each of dataset, include data from all Phase 2, Phase 3 and long-term extension studies. Each dataset should include the following variables:

1. flag for study phase (i.e. 1=Phase 2, 2=Phase 3)
2. study number
3. unique subject ID
4. site ID
5. treatment arm
6. age
7. gender
8. background DMARD medication
9. disposition (i.e. completed, withdrawn, escaped)
10. reason for withdrawal
11. date of withdrawal
12. treatment arm_2 (after escape)
13. date of randomization
14. date of first dose of treatment
15. date of last dose of treatment
16. date of escape
17. start date of escape therapy

18. end date of escape therapy
19. end date from the study (only Phase 2 and Phase 3 programs)
20. duration of exposure to treatment in the original study (only Phase 2 and Phase 3 programs)
 - For placebo patients, you will have two columns (Column 1: total placebo exposure, Column 2: total exposure to active treatment)
21. study duration (only Phase 2 and Phase 3 programs)
22. flag for the event (1=Yes, 0=No) (e.g., for the malignancy dataset, event is malignancy)
23. flag whether event occurred during original study or LTE study (1=original, 2=LTE)
24. diagnosis of the event
25. event date (if multiple events, please provide separate row with the same patient ID and flag)
26. resolution date (only for the infection dataset)
27. flag for LTE (1=Yes, 0=No)
28. date of first dose of treatment in the LTE phase
29. date of last dose of treatment in the LTE phase
30. duration of exposure to active treatment
 - a. original + LTE
 - b. if treatment is different, provide separate columns of the treatment arms
31. duration of actual study (only Phase 2 and Phase 3 programs)
32. treatment arm in the LTE phase
33. disposition in the LTE phase
34. reason for withdrawal in the LTE phase
35. immunoglobulin M, G, A levels for all timepoints measured (a column per timepoint)
36. lymphocyte counts for all timepoints measured (a column per timepoint)

Provide data documentation or data definition file for each of the dataset.

Submit the requested information and datasets as an official response to the NDA by Tuesday, May 29, 2012, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: JBuenconsejo, MSoukup, NNikolov, SYim/ May 21, 2012
cchung/ May 21, 2012

Initialed by: SBarnes/ May 21, 2012

Finalized: cchung/ May 22, 2012

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/s/

CHRISTINE H CHUNG
05/22/2012



NDA 203214

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

ATTENTION: Nickie V. Kilgore, DVM
Director, Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA), dated and received October 21, 2011, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Tofacitinib Tablets, 5 mg and 10 mg.

We also refer to your correspondence dated and received March 30, 2012, requesting review of your proposed proprietary name, Xeljanz. We have completed our review of the proposed proprietary name, Xeljanz and have concluded that it is acceptable.

The proposed proprietary name, Xeljanz, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 30, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christine Chung at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/21/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 15, 2012

To: Nickie Kilgore, DVM, Director, Worldwide Regulatory Strategy	From: Christine Chung, R.Ph. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: N/A	Fax number: 301-796-9728
Email: Nickie.Kilgore@pfizer.com	Phone number: 301-796-3420

Subject: NDA 203214 Tofacitinib- Request for information
Clinical Pharmacology

Total no. of pages including cover: 4

Comments: Please call or send an email to confirm receipt at christine.chung@fda.hhs.gov

Submit requested information by Monday, May 21, 2012

Document to be mailed: YES NO

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are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-3420. Thank you.**

We refer to NDA 203214 for tofacitinib and to your submission dated April 10, 2012, in response to our clinical pharmacology information request. In reviewing the submission, we have following comments and request for additional information:

Results of our analysis for the effect of covariates on calculated secondary parameters, AUC and C_{max} , using parameter estimates from bootstrap runs (provided by you on April 10, 2012), are shown as a forest plot in Figure 1. Comparison of our results with your analysis (Figure 7 from study report pmar-00178) shows that point estimate and 90% CI for C_{max} parameter for Age covariate are not matched, but is similar for all other covariates. To help us understand the reasons for these differences, reevaluate your results and provide confirmation that there is no error in your output with respect to the discrepancy noted above. If differences still exist, provide the exact code you used to generate your output.

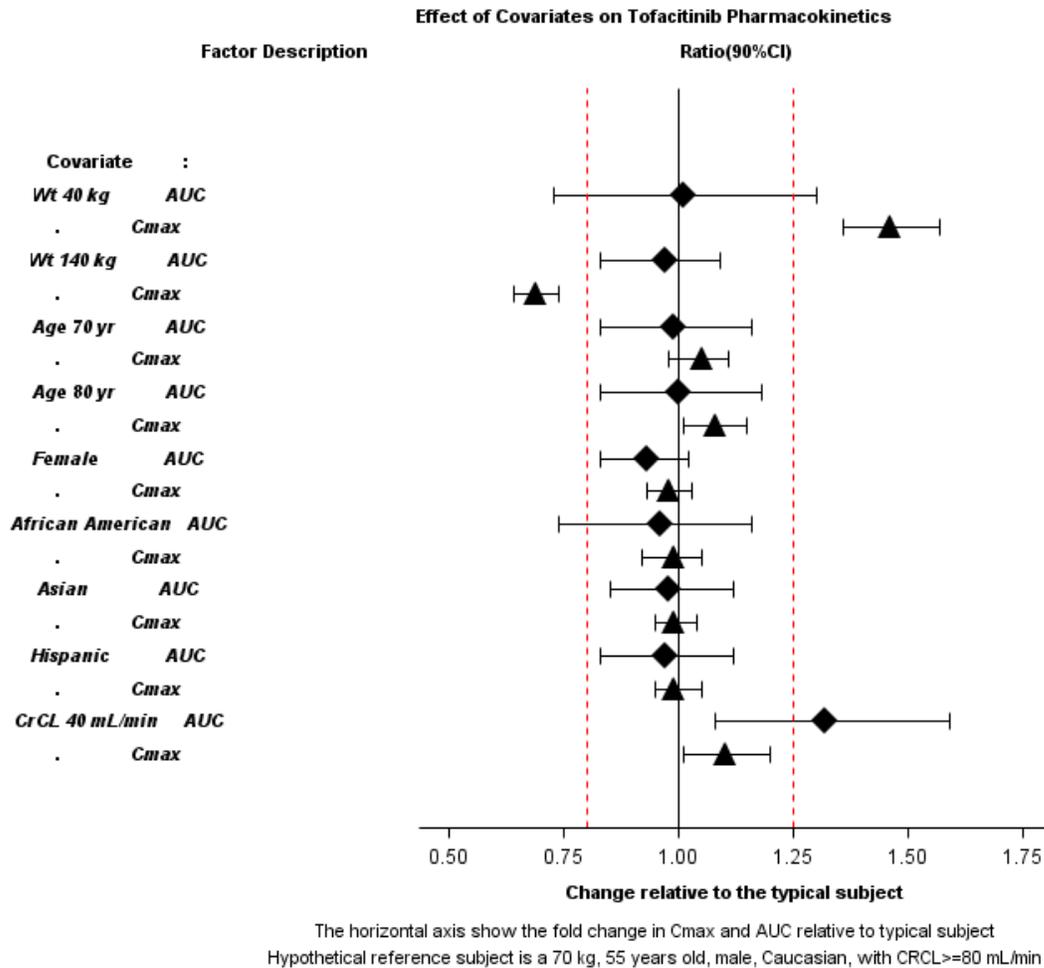


Figure 1: Impact of covariates on pharmacokinetics of tofacitinib (FDA analysis)

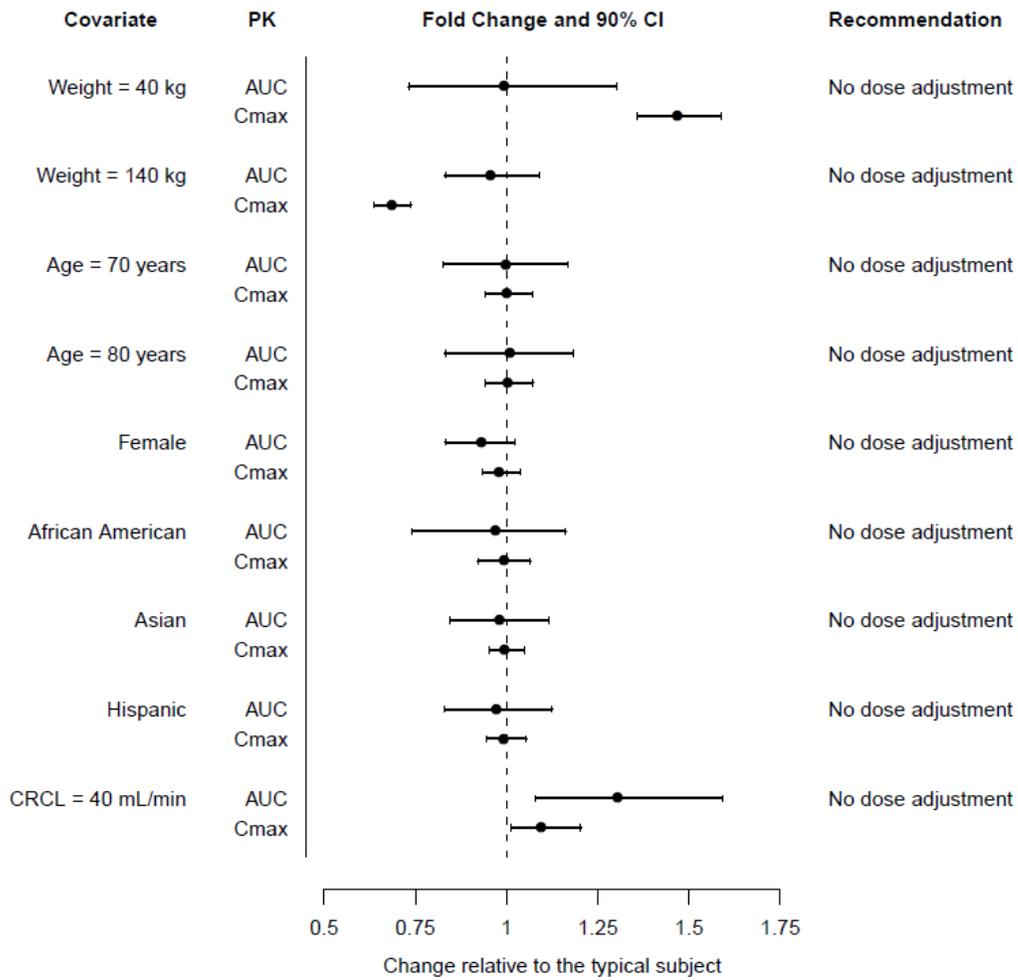


Figure 7 from sponsor's study report pmar-00178

Submit an official response to the NDA by COB Monday, May 21, 2012.
 If you have any questions, please contact Christine Chung at 301-796-3420.

Drafted by: LJain, SDoddapaneni, ABhattaram/ May 15, 2012
cchung/ May 15, 2012

Initialed by: LJafari/ May 15, 2012

Finalized: CChung/ May 15, 2012

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/s/

CHRISTINE H CHUNG
05/15/2012



NDA 203214

**PROPRIETARY NAME
REQUEST WITHDRAWN**

Pfizer, Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, DVM
Director Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) dated October 21, 2011, received October 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib Tablets, 5 mg and 10 mg.

We acknowledge receipt of your April 3, 2012, correspondence, on April 3, 2012, notifying us that you are withdrawing your March 22, 2012, request for a review of the proposed proprietary name, Xeljanz. This proposed proprietary name request is considered withdrawn as of April 3, 2012.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/17/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	Philantha M. Bowen, MPH, RN From: Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE: Please acknowledge receipt.**

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NDA 203214
Tofacitinib
Pfizer, Inc.

We are reviewing your response dated Mar 28, 2012, to our clinical pharmacology information request dated March 26, 2012, regarding population modeling analysis. We have the following comments and requests for further information:

In our analysis, bootstrap on the full model, 502-mod-ctl.txt, for tofapk.xpt dataset using Perl Speaks NONMEM (PsN) and NONMEM 7.2 gives only 243 successful convergence runs out of 1000. However, in step 2 of your response you mention to have achieved 927 successful convergence runs out of 1000. To help us understand the reasons for these different outputs, provide the following:

1. Outline the steps involved in your bootstrap analysis, including the complete details of programs, datasets, and softwares used at each stage
2. Submit the outputs, including all parameter estimates, from all 1000 bootstrap runs in an excel file

Submit an official response to the NDA by COB Tuesday, April 10, 2012.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/4-5-12

Clearance: Jafari/4-5-12
Jain/4-5-12
Shang for Doddapaneni/4-5-12

Finalized: Bowen/4-5-12

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/s/

PHILANTHA M BOWEN
04/05/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha M. Bowen, MPH, RN Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE: Please acknowledge receipt.**

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Your submission dated October 21, 2011, is currently under review. We have the following clinical pharmacology comment and request for information:

Provide a detailed technical description of how the confidence intervals for each factor as shown in Figure 4 of the population modeling analysis report, pmar-00178, were derived separately. For example, describe how the distributions for the weights of 40 kg and 140 kg were separately derived.

Submit an official response to the NDA by COB Wednesday, March 28, 2012.

If there are any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Bowen/3-23-12

Clearance: Jafari/3-23-12
Jain/3-23-12
Doddapaneni/3-26-12

Finalized: Bowen/3-26-12

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/s/

PHILANTHA M BOWEN
03/26/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha Bowen, MPH Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – Statistical Information Request

Total no. of pages including cover: 3

Comments: **TIME-SENSITIVE; Please Acknowledge Receipt**

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Your submission dated October 21, 2011, to NDA 203214 is currently under review. We have the following request for information:

In your Statistical Analysis Plan dated November 10, 2010, to IND 70903, for Study A3921044, you stated that the linear mixed model will be used to analyze change from baseline in the modified Sharp score at Month 6 with treatment and site as fixed effects and actual baseline value as a covariate. Additionally, you planned to conduct sensitivity (robustness) analysis by applying linear mixed model on the ranks with treatment as factor and rank baseline mTSS as covariate.

We were unable to locate the results of the sensitivity analysis for the modified Sharp score in the Study Report. To expedite our review, identify the page number where the results are located in the November submission referenced above or submit the results from this analysis by COB Wednesday, March 28, 2012.

If you have any questions, contact me at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Buenconsejo/3-23-12

Clearance: Jafari/3-26-12

Finalized: Bowen/3-26-12

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/s/

PHILANTHA M BOWEN
03/26/2012



NDA 203214

INFORMATION REQUEST

Pfizer Inc.
Attention: Nickie V. Kilgore, DVM
Director, Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Kilgore:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tofacitinib tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response by April 15th 2012 in order to continue our evaluation of your NDA.

1. In the presentation of the risk assessment approach for Drug substance and Drug product, terminology was used that includes (b) (4)



Drug substance:

2. Description of the drug substance manufacturing process is restricted to critical/key parameters in relation to a few critical steps. This is neither sufficient nor in line with current regulation. The description of the manufacturing process represents the applicant's commitment for the manufacture of the active substance. Therefore, adequate information should be provided to describe all manufacturing steps and process controls, including but not limited to all critical and non-critical parameters (with their target values), current and planned commercial manufacturing scale, in-process controls (b) (4) [redacted] Updated section 3.2.S.2.2 (narrative and flow chart) should therefore be presented.
3. [redacted] (b) (4). The Agency recognizes that changes to non-critical process parameters beyond the ranges provided in the application, can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes beyond the ranges applied for in the submission, including changes to non critical process parameters, should be provided to the Agency via the appropriate mechanism.
4. Include a test and acceptance criterion for assay in the specification for [redacted] (b) (4).
5. Revise the specifications for the proposed [redacted] (b) (4) starting materials for the synthesis of [redacted] (b) (4), to identify the "appropriate" [redacted] (b) (4) methods that are used for confirming the identity of each material and provide assurance that these are specific (e.g. [redacted] (b) (4)), not non-specific ([redacted] (b) (4)) methods.
6. It is noted that the manufacturing processes listed in S.2.6 for the proposed starting materials [redacted] (b) (4) are called "examples." Provide a description of your control strategy in cases where the syntheses of the starting materials might be changed to provide assurance that you will be assessing the fate of any new starting material impurities and whether or not they do impact the final impurity profile, and hence, the quality and safety of the drug substance.
7. Provide confirmation that the intermediate [redacted] (b) (4) is [redacted] (b) (4) [redacted] (b) (4). If that is the case, provide the specification that is applied to this [redacted] (b) (4) intermediate.
8. [redacted] (b) (4) should be considered as critical quality attributes as they will have a direct impact on the safety and efficacy of the product.
9. As the control of the [redacted] (b) (4) starting material is important to the control of the [redacted] (b) (4) of the drug substance, submit the [redacted] (b) (4)

method and the associated validation data to the application.

10. Revise the control strategy summary table S.2.6-15 to include the pertinent information for the (b) (4) attribute.
11. Revise the acceptance criterion for each of the following drug substance specified impurities to not more than (b) (4) as you have not provided sufficient individual data to qualify these at a (b) (4) from a toxicological perspective: (b) (4)
(b) (4) Alternatively, you may provide supporting toxicological data.
12. The formula used for the calculation of the percentage of individual impurities in the (b) (4)
(b) (4) Revise that section of the method accordingly.
13. The (b) (4) in contact with the active substance tofacitinib citrate should be in compliance, as a minimum, with the relevant regulations related to (b) (4)
(b) (4) as per title 21 CFR.
14. Regarding the post-approval stability protocol, assay should be included in the monitored parameters. In addition, a commitment should be provided to continue the long-term stability studies for the proposed re-test period.
15. (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
16. (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
17. It is not clear why resolutions between (b) (4), between (b) (4) and between (b) (4) have not been studied. Resolution between the impurities should be verified all over the final proposed (b) (4) provided. The (b) (4) study results were not assessed with regard to specificity, accuracy, precision, linearity and LOQ/LOD to ensure suitable method performance at each of the experimental conditions.

18. [REDACTED] (b) (4)

Drug Product:

19. The predictability of the drug substance particle size distribution model is considered neither accurate nor validated by tofacitinib drug development or registration batch data. Therefore, your proposed acceptance criterion for the drug substance particle size of [REDACTED] (b) (4) of NMT [REDACTED] (b) (4) based on the model prediction is not acceptable. [REDACTED] (b) (4) the acceptance criterion to be in line with the range of the batch data demonstrated in the submission.

20. Description of the drug product manufacturing process is restricted to critical/key parameters in relation to few critical steps. This is neither sufficient nor in line with current regulation. The description of the manufacturing process represents the applicant's commitment for the manufacture of the drug product. Therefore, adequate information should be provided to describe all manufacturing steps and process controls, including all critical and non-critical parameters (with their target values). To meet the regulatory requirements, your options are as follows:

In accordance with 21CFR 314.50(d)(ii)(c),

Provide a master batch record to any section of module 3, with a reference/link to the master batch record in the process description (section P.3.3)

or

Provide a process description to section P.3.3 that is comparably detailed to the master batch record.

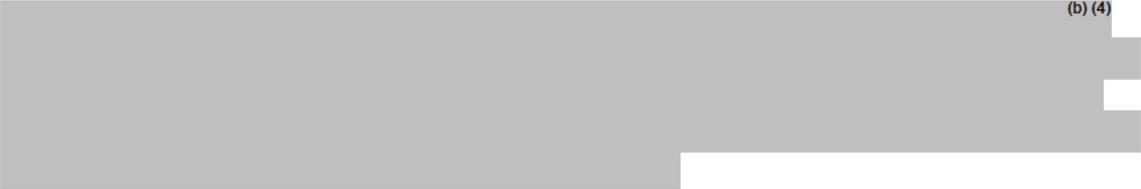
21. Your proposed acceptance criteria of NMT [REDACTED] (b) (4) for specified degradants [REDACTED] (b) (4) and [REDACTED] (b) (4), respectively, are not supported by the batch data (including clinical batches). [REDACTED] (b) (4) has never been [REDACTED] (b) (4) the reporting threshold of [REDACTED] (b) (4) and [REDACTED] (b) (4) has never been [REDACTED] (b) (4) in all batches at all time points during stability. Per ICH guidance Q3B(R) these two impurities should be categorized as unspecified impurity with NMT [REDACTED] (b) (4) limit. Revise your proposed acceptance criteria accordingly.

22. Your proposed acceptance criterion of NMT [REDACTED] (b) (4) for the total impurities is not supported by the batch data. The total impurities in the drug product have never been [REDACTED] (b) (4) than [REDACTED] (b) (4) for all batches at all time points during stability. [REDACTED] (b) (4) the acceptance criterion for the total impurities to reflect the actual batch experience, including clinical batches.

23. For drug product you have proposed both [REDACTED] (b) (4) methods for identification, assay and content uniformity test. Describe the criteria by which the [REDACTED] (b) (4)

methods will be used. In the specification sheet:

- a. Clearly state which method is the regulatory method that will be used for confirmation of product quality post product release.
- b. Clearly state which method will be used for routine product release.

24.  (b) (4)

25. Any post-marketing labeling change (including package counts) needs to be reported to the Agency. You are advised to submit labeling for all potential marketing container closure configurations (e.g., number of tablets in a container) in the NDA even if some of them may not be used at launch.

26. Your proposed protocol for annual stability test of the drug product is not acceptable because it does not include test for assay. Revise the protocol to include the assay test.

27. In order to ensure that stability of tofacitinib film-coated tablets is independent of movement within the proposed design space, indicate if the batches considered in the ongoing registration stability studies were manufactured at target or at different regions within the proposed commercial scale design space. Additionally, it is recommended to include in your post approval stability program plans to monitor stability of batches manufactured at commercially unverified areas of the design space.

28.  (b) (4)

 (b) (4)

- b.
- c.
- d.

(b) (4)

31. Regarding

(b) (4) assay method:

- a.
- b.
- c.

(b) (4)

32. Regarding 5 mg and 10 mg

(b) (4) assay methods provide the following information:

- a.
- b.
- c.
- d.
- e.

(b) (4)

33. Regarding validation of tablet assay methods, describe what statistical test was used to establish equivalency on (b) (4) and the reference methods.

(b) (4)

Biopharmaceutics

36. Your proposal of using the disintegration test in lieu of the dissolution test is acceptable. However, the proposed acceptance criterion of (b) (4) is not acceptable; your data support an acceptance criterion of (b) (4). Implement this criterion and provide a revised specification table for your drug product.

(b) (4)
(b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
03/16/2012
Signed for Eric Duffy

Executive CAC

Date of Meeting: March 6, 2012

Committee: Abigail Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Adebayo Lanionu, Ph.D., DMIP, Alternate Member
Molly Shea, Ph.D., DPARP, Nonclinical Supervisor
Steven Leshin, D.V.M., Ph.D., DPARP, Presenting Reviewer

Author of Draft: Steven Leshin

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #203214

Drug Name: CP-690,550 (tofacitinib)

Sponsor: Pfizer

Background:

CP-690,550 (tofacitinib) is a new molecular entity, small molecule kinase inhibitor being developed for the treatment of rheumatoid arthritis. It is an immunosuppressant that targets Janus kinase 3 (JAK3), but has inhibitory activity on JAK1 and JAK2. The immunosuppression is mediated through the suppression in immune cells of JAK cytokine signaling, preventing the subsequent activation of signal transducers and activators of transcription.

Tg.rasH2 Mouse Carcinogenicity Study

There was no evidence for CP-690,550-related oncogenic potential in rasH2 (hemizygous) mice that received CP-690,550 via oral gavage in 0.5% methylcellulose in reverse osmosis deionized water for 6 months at dose levels of 25, 75, and 200 mg/kg/day. Clinical signs (hypoactivity, recumbency) were observed at 75 and/or 200 mg/kg/day. No incidence of tumors or tumor combinations was statistically significantly different from vehicle control in any of the CP-690,550 treated groups. CP-690,550-related, nonneoplastic microscopic findings were present in the femoral bone marrow (focal subphyseal hypocellularity characterized by an increased prominence of adipocytes) of males at 75 and 200 mg/kg/day and females at 200 mg/kg/day and in the spleen (cellular depletion, red pulp) of males at 75 and 200 mg/kg/day and females at 200 mg/kg/day.

Toxicokinetic analysis during week 20 of the 26-week study, demonstrated increasing C_{max} and AUC_{0-24} with increasing CP-690,550 dose and no gender differences. At the NOAEL for CP-690,550-induced malignancy, 200 mg/kg/day, the gender-averaged parameters were T_{max} 0.75 hr, C_{max} 5765 ng/mL, and AUC_{0-24} 17250 ng-h/mL.

Comparison of drug exposure for the mouse with the estimated human AUC₀₋₂₄ of 550 ng-h/mL for the maximal dose of 20 mg/day, results in an approximate 32-fold exposure margin.

Rat Carcinogenicity Study

In a 2-year carcinogenicity study, Sprague-Dawley rats were administered CP-690,550 in 0.5% methylcellulose in reverse osmosis deionized water by oral gavage at doses of 10, 30, and 75 mg/kg/day. The female high dose was initially 100 mg/kg/day, but then reduced to 75 mg/kg/day during week 19 due to mortalities related to bacterial infections. Surviving males administered 75 mg/kg per day were killed during week 94 and all surviving males from the remaining groups during week 98 of dosing. The 26-week toxicokinetic values for the 75 mg/kg/day dose in this study were similar to values in the male and female 100 mg/kg/day dose of the 6-month general toxicology study. In both studies, CP-690,550 AUC exposure was higher in females than males.

CP-690,550-related neoplastic findings (see table below) tended to be gender specific and included:

- interstitial cell adenomas in testis at ≥ 30 mg/kg/day
- benign thymomas in females at 100/75 mg/kg/day
- malignant hibernomas for females at ≥ 30 mg/kg/day

Gender	Males				Females			
	1	2	3	4	1	2	3	4
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	10	30	75	0	10	30	100/75*
Malignancy								
number examined	70	60	60	70	67	60	57	63
Testis								
interstitial cell adenoma	1	2	4	14	-	-	-	-
Body, whole/cavity								
malignant hibernoma	1	0	1	2	0	2	5	4
number examined	69	59	58	66	67	60	57	63
Thymus								
benign thymoma	1	0	0	1	0	1	1	4
malignant thymoma	0	0	1	0	1	0	1	0
combined	1	0	1	1	1	1	2	4

- Not applicable

* Dose reduced on day 133

The NOAEL for carcinogenicity in males and females was 10 mg/kg/day corresponding to an AUC₀₋₂₄ of 3880 ng-hr/mL and 7850 ng-hr/mL, respectively, based on week 26 toxicokinetic results. This provided a 7-fold exposure margin (using the low value of 3380 ng-hr/mL) over the maximal proposed human dose of 10 mg b.i.d. (20 mg/day, corresponding to approximately 550 ng-h/mL).

CP-690,550-related, nonneoplastic microscopic findings included increased incidences of decreased cellularity of lymphocytes in lymphoid tissues (spleen, thymus, mesenteric and

inguinal lymph nodes, and Peyer's patch of the intestine); decreased extramedullary hematopoiesis, decreased pigment, and increased sinusoidal dilatation in the spleen; marginally decreased cellularity in the bone marrow (sternum only); and increased incidence and severity of alveolar proteinosis and alveolar macrophage infiltrates in the lung of males and females. Decreased lymphocyte cellularity was attributed to an expected pharmacologic immunomodulatory effect of CP-690,550 on the lymphoid/hematopoietic tissues.

Executive CAC Recommendations and Conclusions:

Tg.rasH2 Mouse:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee concurred that the study was acceptable, despite the urinary tract infections in males and females at the high dose.
- The Committee concurred that the following were drug related neoplasms: interstitial cell tumors in the testis of males; benign thymomas in the thymus of females; and malignant hibernomas in females (a rare tumor not meeting statistical significance, but seen at a higher than usual incidence). The Committee noted that the mechanism of action studies support the hibernomas as being pharmacologically plausible.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DPARP
/MShea/Nonclinical Supervisor, DPARP
/LLeshin/Reviewer, DPARP
/PBowen/CSO/PM, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
03/08/2012

ABIGAIL C JACOBS
03/08/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Type of Meeting: Proprietary Name Review

Meeting Date: February 28, 2012; 11:15 AM
Meeting Location: FDA White Oak, Bldg 22, Room 4266, Teleconference

Application: NDA 203214
Proposed Proprietary Name: (b) (4)
Established Name: Tofacitinib Citrate
Applicant: Pfizer

Meeting Chair: Lubna Merchant, Team Leader, DMEPA
Meeting Recorder: Nichelle Rashid, Safety Regulatory Project Manager

FDA Attendees:

Office of Surveillance and Epidemiology
Carol Holquist, Director, DMEPA
Lubna Merchant, Team Leader, DMEPA
Carlos Mena-Grillasca, Safety Evaluator, DMEPA
Lissa Owens, Safety Evaluator, DMEPA
Nichelle Rashid, Safety Regulatory Health Project Manager
Frances Fahnbulleh, Safety Regulatory Health Project Manager

Applicant Attendees:

Pfizer
Nickie Kilgore, DVM
Director, Worldwide Regulatory Strategy

Thomas E. Ruth
Director, Trademark Development, Global Commercial Operations

Michael Quinlan,
Manager, Trademark Development, Global Commercial Operations

Christine Kobryn, PhD,
Associate Director, Worldwide Regulatory Strategy

Background:

DMEPA completed review of the proposed proprietary name (b) (4) under IND 070903, (OSE RCM #2010-2480 dated May 4, 2011); and found the name conditionally acceptable at that time. Per FDA Guidance for Industry, the proposed proprietary name, (b) (4), was re-submitted for review under the NDA 203214 on October 25, 2011, and found unacceptable (OSE RCM 2011-4192 dated January 20, 2012) due to (b) (4)

The Applicant requested a teleconference with DMEPA to better understand the concern with the cited name so they can focus their reconsideration response appropriately.



(b) (4)

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

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/s/

NICHELE E RASHID
04/05/2012



NDA 203214

**METHODS VALIDATION
MATERIALS RECEIVED**

Pfizer Inc.
Attention: Nickie V. Kilgore, DVM
Director Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [REDACTED]^{(b) (4)} (tofacitinib) tablets, 5 & 10 mg and to our 1/27/2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 2/24/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
02/27/2012



NDA 203214

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Pfizer Inc.
Attention: Nickie V. Kilgore, DVM
Director Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (tofacitinib) tablets, 5 & 10 mg.

We will be performing methods validation studies on (b) (4) (tofacitinib) drug substance CP-690,550 as described in NDA 203214.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Identity, assay, and purity evaluation of CP-690,550-10 drug substance by reversed-phase liquid chromatography

Samples and Reference Standards

(b) (4)

Equipment (These will be returned)

1 Acquity UPLCBEH C18 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy
1114 Market Street, Room 1005A
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
Chemist
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
01/27/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: January 26, 2012

To: Nickie Kilgore, DVM Director, Worldwide Regulatory Strategy	From: Philantha M. Bowen, MPH, RN Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 860-686-7545	Fax number: 301-796-9728
Phone number: 860-441-5030	Phone number: 301-796-2466

Subject: NDA 203214 – FDA Information Request re: Programming Error

Total no. of pages including cover: 4

Comments: Please acknowledge receipt.

Document to be mailed: YES NO

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NDA 203214
Tofacitinib
Pfizer, Inc.

Your submission dated October 21, 2011, is currently under review. In an email communication dated January 19, 2012, you reported on a recently identified programming error “*related to the calculation of the 4 component Disease Activity Score (DAS28-4(ESR)) and its derivative values; specifically, the Physician Global Assessment score was included in the calculation instead of the Patient Global Assessment score, resulting in incorrect values of the DAS28-4(ESR) included in the application package.*”

You further state that:

“We have determined that this error was a consequence of a data transcription error.”

This raises questions about the integrity of the database in this application. Therefore, we have the following request for information:

1. Clarify whether or not an error occurred in transcribing the raw data for both Physician and Patient/Subject Global Assessment?
2. Explain if the error is systematic (i.e. all baseline and subsequent values were transcribed incorrectly) or if some were incorrect and others were transcribed correctly?
3. Confirm if the ACR response rates were affected by this error, i.e. whether Physician and Patient Global Assessments (baseline and subsequent values) were transcribed correctly and whether ACR response rates are calculated correctly.
4. Confirm that the programming errors do not affect any of the population based analysis or other parts of clinical pharmacology data.

Submit an official response to the NDA by Tuesday, January 31, 2012.

NDA 203214
Tofacitinib
Pfizer, Inc.

If there are any questions, contact Philantha Bowen, Senior Regulatory Management Officer, at 301-796-2466.

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Drafted: Nikolov/1-26-12

Clearance: Barnes/1-26-12

Finalized: Bowen/1-26-12

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/s/

PHILANTHA M BOWEN
01/26/2012



NDA 203214

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Pfizer, Inc.
445 Eastern Point Road
Groton, Connecticut 06340

ATTENTION: Nickie V. Kilgore, DVM
Director, Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) dated October 21, 2011, received October 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib Tablets, 5 mg and 10 mg.

We also refer to your October 25, 2011, correspondence, received October 25, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
01/23/2012



NDA 203214

FILING COMMUNICATION

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, DVM, Director
Worldwide Regulatory Strategy

Dear Dr. Kilgore:

Please refer to your New Drug Application (NDA) dated October 21, 2011, received October 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Tofacitinib.

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 August 21, 2012.

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 July 3, 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.

We request that you submit the following information:

- Submit the coding dictionary used for mapping investigator verbatim terms to preferred

terms. If submitting as a PDF document, include mapping in both directions (verbatim -> preferred and preferred -> verbatim).

- Provide definitions for the following terms as they are used in the CMC section of the NDA: Design Space, Knowledge Space, Operational Boundaries, Operational Space, and Reaction Space.

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

Highlights:

1. The verbatim statement “Initial U.S. Approval” should be followed by the 4-digit year. *Insert 2012.*
2. The revision date at the end of the Highlights section is the month/year of application or supplement approval. *Insert Revised: 08/2012*

Full Prescribing Information:

3. In Section 17: Patient Counseling Information, *add the wording as follows:*

“See FDA-approved patient labeling (Medication Guide)”
4. The revision date at the end of the Highlights Section replaces the “revision” date at the end of the full prescribing information and should not appear in both places.
5. Logos should not appear in the SPL file. *Remove* the logo from the end of the Full Prescribing Information in the SPL file.

We request that you resubmit labeling that addresses these issues by January 13, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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.

We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and partial deferral requests are denied.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
12/19/2011



NDA 203214

NDA ACKNOWLEDGMENT

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Nickie V. Kilgore, DVM, Director
Worldwide Regulatory Strategy

Dear Dr. Kilgore:

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

Name of Drug Product: Tofacitinib Tablets 5 mg, 10 mg

Date of Application: October 21, 2011

Date of Receipt: October 21, 2011

Our Reference Number: NDA 203214

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 December 20, 2011, 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 Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Senior Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHILANTHA M BOWEN
11/01/2011