

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208246Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208246

SUPPL #

HFD #

Trade Name Xeljanz Extended Release Tablets

Generic Name Tofacitinib Extended Release Tablets

Applicant Name Pfizer, Inc.

Approval Date, If Known: February 24, 2016

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)

b) 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.

The Applicant did not include any new clinical efficacy/safety information. This application is cross-referenced to NDA 203214, tofacitinib immediate release tablets for efficacy/safety. The extended release clinical program included seven Phase I biopharmaceutic studies in healthy volunteers. The Applicant also provided exposure response analysis to establish the relevant PK parameter to bridge efficacy.

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:

c) Did the applicant request exclusivity?

YES NO

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

d) 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# 203214

Tofacitinib Immediate Release Tablet

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

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

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

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

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

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

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

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

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

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

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

YES NO

If yes, explain:

=====

Name of person completing form: Sadaf Nabavian
Title: Regulatory Project Manager
Date: February 16, 2016

Name of Office/Division Director signing form: Dr. Sarah Yim
Title: Supervisory Associate Director

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

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

/s/

SADAF NABAVIAN
02/23/2016

SARAH K YIM
02/23/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208246 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Xeljanz Extended Release Established/Proper Name: Tofacitinib Extended Release Dosage Form: Tablet		Applicant: Pfizer, Inc. Agent for Applicant (if applicable):
RPM: Sadaf Nabavian		Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: 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.</i>	
❖ Actions		
- Proposed action - User Fee Goal Date is <u>February 24, 2016</u> - Previous actions <i>(specify type and date for each action taken)</i>		☒ AP ☐ TA ☐ CR ☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): New Dosage Form (Type 3)
(confirm chemical classification at time of approval)

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

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s)
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included 2/11/2016
• Original applicant-proposed labeling	☒ Included 4/24/2015
❖ 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>	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included 2/11/2016
• Original applicant-proposed labeling	☒ Included 4/24/2016
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	☒ Included 1/8/2016
❖ Proprietary Name • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i>	Accepted; 6/25/2015 OSE Review; 6/24/2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☒ None 7/1/2015 DMEPA: ☒ None 1/19/2016 DMPP/PLT (DRISK): 2/19/2016, 2/10/2016 ☐ None OPDP: ☒ 2/11/2016 None SEALD: ☐ None X CSS: ☐ None X Product Quality ☐ None X Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	RPM Filing Review: 7/2/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included (to be signed after approval action)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - 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>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>1/6/2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	2/12/2016, 2/11/2016, 1/28/2016; 1/21/2016, 1/15/2016, 11/12/2015, 8/6/2015, 7/1/2015, 6/10/2015, 5/6/2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	MCP memo to file: 2/17/2016 PeRC MM: 1/26/2016 OSI Memo: 7/27/2015
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 12/18/2014 No mtg
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 2/21/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 3 (2/19/2016)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☐ No separate review
• Clinical review(s) (indicate date for each review)	1/20/2016, 6/23/2015
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Clinical Review dated 2/22/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☐ None To be placed by Reviewer
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☒ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☐ No separate review
Statistical Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☐ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 1/21/2016, 6/23/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☐ None requested 7/27/2015

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 1/20/2016, 6/11/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☐ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None 2/11/2016, 2/10/2016, 9/18/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Quality Assessment/OPQ Review, Page 185
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable 1/25/2016 Re-evaluation date (b) (4) ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

SADAF NABAVIAN
03/01/2016

From: [Raman, Reena](#)
To: [Nabavian, Sadaf](#)
Subject: ORP Consult on NDA 208246 for ER tofacitinib
Date: Wednesday, January 20, 2016 11:43:39 AM

DPARP requested a consult from ORP on the acceptability, from a regulatory perspective, of Pfizer Inc.'s proposed extended-release (ER) tofacitinib product submitted in NDA 208246. The consult request states that Pfizer is the holder of NDA 203214 for the immediate-release (IR) tablet formulation of tofacitinib, approved in November 2012. The clinical development of the ER formulation is based on establishing bioequivalence to the IR formulation. The consult states that the dose of the IR formulation is 5 mg taken twice daily, for a total daily dose of 10 mg. In contrast, the dose of the proposed ER formulation is 11 mg taken once daily. The consult request notes further that 21 CFR 320.23(b) states: "Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered **at the same molar dose** of the active moiety under similar experimental conditions, either single dose or multiple dose" (emphasis added). Accordingly, DPARP requests ORP's input on the acceptability, from a regulatory perspective, of approving the ER tofacitinib product with a nominal dose different from the nominal dose of the IR formulation of tofacitinib.

My understanding is that Pfizer submitted NDA 208246 for an ER tofacitinib product as a 505(b)(1) application cross-referencing its own NDA 203214 for the IR tofacitinib product. Unlike for ANDAs, there is no statutory or regulatory requirement that a 505(b)(1) NDA establish bioequivalence consistent 21 CFR 320.23(b). Therefore, from a regulatory policy perspective, the proposed ER tofacitinib product appears acceptable, and there is no regulatory barrier to approving the ER formulation even though it has a different nominal dose as compared to the IR formulation.

I hope this helps. If you have any further questions, please let me know.

Thank you,
Reena

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

/s/

SADAF NABAVIAN
02/17/2016



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 12, 2016

To: Gary F. Perry Director Worldwide Regulatory Affairs	From: Sadaf Nabavian Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax #: (860) 686-5986	Fax number: 301-796-9728
Phone number: (860) 441-6498	Phone number: 301-796-2777
Subject: NDA 208246; FDA Labeling Comments	

Total no. of pages including cover: 3

Comments: Please confirm receipt.

Document to be mailed: YES NO X

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NDA 208246
Xeljanz XR
Pfizer, Inc.

Dear Mr. Perry:

Your submission dated April 24, 2015, for Xeljanz XR tablet is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by COB Thursday, February 18, 2016, followed by official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

(See appended electronic signature)

Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager

Drafted by: SNabavian/2.12.2016

Cleared by: LJafari/2.12.2016

Finalized by: SNabavian/2.12.2016

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

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/s/

SADAF NABAVIAN
02/12/2016



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 11, 2016

To: Gary F. Perry Director Worldwide Regulatory Affairs	From: Sadaf Nabavian Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax #: (860) 686-5986	Fax number: 301-796-9728
Phone number: (860) 441-6498	Phone number: 301-796-2777
Subject: NDA 208246; FDA Comments	

Total no. of pages including cover: 3

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NDA 208246
Tofacitinib XR
Pfizer, Inc.

Dear Mr. Perry,

We refer you to your submission dated January 29, 2016, in response to our request to revise your pediatric formulation development time lines. We have described and listed the proposed post-marketing requirements (PMR) and are requesting your agreement to these PMRs including the milestone dates. Provide your proposal for Study Completion dates for the three studies:

Study 1: Conduct a study in adult healthy volunteers to assess the pharmacokinetics and bioavailability of multiple age-appropriate tofacitinib XR formulations compared to the tofacitinib IR formulation.

Protocol Submission date:	December 2016
Study Completion date:	Provide date
Final Report Submission date:	September 2017

Study 2: Conduct a pharmacokinetic study in adult healthy volunteers comparing multiple tofacitinib XR formulations to the tofacitinib IR formulations to select a suitable age-appropriate tofacitinib XR formulation that meets the target pharmacokinetic profile.

Protocol Submission date:	March 2018
Study Completion date:	Provide date
Final Report Submission date:	January 2019

Study 3: Conduct a pharmacokinetic study in adult healthy volunteers to establish the equivalence of AUC and similarity in other pharmacokinetic parameters between the proposed commercial age-appropriate tofacitinib XR formulation and tofacitinib IR formulation.

Protocol Submission date:	July 2019
Study Completion date:	Provide date
Final Report Submission date:	May 2020

Submit your responses via email to Sadaf.Nabavian@fda.hhs.gov by noon, February 16, 2016, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/2.11.2016
Cleared by: Ladan Jafari/2.11.2016
JWaheed/NNikolov/2.11.2016
Finalized by: SNabavian/2.11.2016

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/s/

SADAF NABAVIAN
02/11/2016



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 28, 2016

To: Gary F. Perry Director Worldwide Regulatory Affairs	From: Sadaf Nabavian Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax #: (860) 686-5986	Fax number: 301-796-9728
Phone number: (860) 441-6498	Phone number: 301-796-2777
Subject: NDA 208246; FDA Labeling Comments	

Total no. of pages including cover: 41

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NDA 208246
Xeljanz XR
Pfizer, Inc.

Dear Mr. Perry:

Your submission dated April 24, 2015, for Xeljanz XR tablet is currently under review. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by noon, February 4, 2016, followed by official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

(See appended electronic signature)

Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager

Drafted by: SNabavian/1.28.2016

Cleared by: LJafari/1.28.2016

Finalized by: SNabavian/1.28.2016

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/s/

SADAF NABAVIAN
01/28/2016

**PeRC Meeting Minutes
January 6, 2015**

PeRC Members Attending:

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Raquel Tapia

Gil Burckart

Andrew Mulberg [Redacted] Non Responsive

Thomas Smith

Daiva Shetty (Did not review [Redacted] Non Responsive Tofacitinib [Redacted] Non Responsive

Meshawn Payne

Gregory Reaman (Did not review Tofacitinib [Redacted] Non Responsive

Dianne Murphy

Adrienne Hornatko-Munoz

Michelle Roth-Kline

Rosemary Addy

Gerrie Baer

Maura O'leary

Wiley Chambers

Rachel Witten

Shrikant Pagay

Gettie Audain

Agenda

8:30	Non Responsive				
9:30	Non Responsive				
9:40	Non Responsive				
9:50	Non Responsive				
10:00	Non Responsive				
10:10	Non Responsive				
10:30	Non Responsive				
10:50	Non Responsive				
11:20	Non Responsive				
11:40	Non Responsive				
11:50	NDA 208246	Tofacitinib Partial Waiver/Deferral/Plan (with Agreed iPSP)	DPARP	Sadaf Nabavian	JIA
12:00	Non Responsive				
	Non Responsive				
	Non Responsive				

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Tofacitinib XR Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Proposed Indication: (b) (4)
- This product triggers PREA as a new active ingredient and has a PDUFA goal date of February 24, 2016.
- The Division noted that the plan remains the same as the plan agreed upon in the Agreed iPSP.
- The division also noted that pediatric studies for the IR preparation are already required under PREA and are ongoing. The pediatric plan for this product will rely on demonstration of efficacy for the IR product. The division noted that formulation development for the MR preparation will need to be performed for patients who require a dose less than 11 mg. The PeRC recommended that the formulation development proceed accordingly and not be delayed.
- *PeRC Recommendations:*
 - The PeRC agreed with the division to grant a partial waiver in patients birth to 23 months because studies are impossible or highly impractical and to the deferral in patients 2 years to 17 years as outlined in the agreed iPSP.
 - The PeRC recommends that the division modify timelines for PREA requirements so that the sponsor can proceed with formulation development without delay (see comments above).

Non Responsive

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/s/

GEORGE E GREELEY
01/26/2016



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 21, 2016

To: Gary F. Perry Director Worldwide Regulatory Affairs	From: Sadaf Nabavian Sr. Regulatory Project Manager
Company: Pfizer, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax #: (860) 686-5986	Fax number: 301-796-9728
Phone number: (860) 441-6498	Phone number: 301-796-2777
Subject: NDA 208246; FDA Information Request	

Total no. of pages including cover: 3

Comments: Please confirm receipt.

Document to be mailed: YES NO X

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this communication is not authorized. If you have received this document
in error, please notify us immediately by telephone at (301) 796-2300.
Thank you.

NDA 208246
Tofacitinib XR
Pfizer, Inc.

Dear Mr. Perry,

Your NDA 208246 submitted on April 24, 2015, is currently under review. We have the following comments and requests for information:

In your pediatric study plan amendment submitted on June 15, 2015, you request a deferral for the pediatric assessment to address PREA requirements. You further propose the following:

- Development of an age-appropriate extended release formulation for patients who require a dose less than 11 mg:

Anticipated Timelines	Activity (Duration)
April 2015 - June 2016	 (b) (4)
July 2016 - November 2017	
October 2017 – March 2018	
April 2018 – June 2019	
June 2019 – November 2019	
December 2019 – June 2020	
July 2020 – July 2021	
July 2020 – September 2021	

MR=Modified Release; QD=Once Daily; PK=Pharmacokinetics; BA=Bioavailability.
a. Duration includes clinical supply manufacture

- Proposed clinical studies to support this development:



Your proposed milestones are excessively long. Given that the efficacy and safety data in PJIA with the immediate release formulation are expected to be available by 2018, revise your milestones to shorten the development of the modified release formulation in pediatric patients. Submit a revised timeline for the initiation of each phase of pediatric product development, and clinical studies via email to Sadaf.Nabavian@fda.hhs.gov by COB Wednesday, January 27,

2016, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: NNikolov/1.20.2016
Cleared by: Ladan Jafari/1.20.2016
Finalized by: SNabavian/1.21.2016

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/s/

SADAF NABAVIAN
01/21/2016



NDA 208246

INFORMATION REQUEST

Pfizer Inc.
Attention: Gary F. Perry
Director, Worldwide Safety and Regulatory
445 Eastern Point Road
Groton, CT 06340

Dear Mr. Perry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib (CP-690,550) Modified Release 11 mg Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, by January 21, 2016, in order to continue our evaluation of your NDA.

As per our discussion during the 1/12/16 teleconference, your IVIVC model as proposed is not acceptable. We sent you the IVIVC model developed by the FDA using Phoenix software (Version 6.4) for your consideration and your review.

1. The FDA conducted an independent internal analysis of the IVIVC model based on the data with some modifications (excluded subject # 10011099, used actual dissolution data up to 6 hour time point (not predicted data), considered slow and fast profiles for internal validation, target and MR 22 for external validation) and summary report you submitted, and found that the dissolution acceptance criteria as proposed by you are not acceptable. The FDA recommends that you resubmit your IVIVC analysis considering the data included in Phoenix project file.
2. Even though the reconstructed model is adequate, it is not able to support a dissolution acceptance criteria beyond (b)(4)% variation because the difference in predicted AUC between the slow and fast formulations is (b)(4)%. We recommend the following dissolution acceptance criteria for Tofacitinib MR Tablets, 11mg based on the dissolution data:

1 hour: NMT (b)(4)%
2.5 hours: (b)(4)%
6 hours: NLT (b)(4)%

Note: Your proposed acceptance criteria which are based on the upper and lower bounds being BE to the target (clinical formulation) is not acceptable (refer to the IVIVC guidance for more details on how to set dissolution acceptance criteria in the presence of

an acceptable IVIVC). Also, we remind you that setting dissolution acceptance criteria bounds based on extrapolation is not acceptable.

3. Implement the above recommended dissolution acceptance criteria and submit the updated specifications table in an amendment to the NDA.
4. Re-assess your manufacturing process development studies to determine whether the revised dissolution specification (1h: NMT $\frac{(b)}{(4)}\%$; 2.5h: $\frac{(b)}{(4)}\%$; 6h: NLT $\frac{(b)}{(4)}\%$) has any impact on the PARs that were set based on the previous dissolution specification (1h: NMT $\frac{(b)}{(4)}\%$; 2.5h: $\frac{(b)}{(4)}\%$; 6h: NLT $\frac{(b)}{(4)}\%$).

If you have any questions, call Giuseppe Randazzo, Office Director (Acting), Office of Program and Regulatory Operations, serving as the Regulatory Business Process Manager (RBPM), at (301) 796-3277.

Sincerely,

Tanya D. Clayton -A

Digitally signed by Tanya D. Clayton -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300213184,
cn=Tanya D. Clayton -A
Date: 2016.01.15 14:33:08 -05'00'

Signing on behalf of Giuseppe Randazzo, MS
Office Director (acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration



NDA 208246

INFORMATION REQUEST

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Gary F. Perry
Director, Worldwide Safety and Regulatory

Dear Mr. Perry:

Please refer to your New Drug Application (NDA) dated April 24, 2015, received April 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib (CP-690,550) Modified Release 11 mg Tablets.

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

1. Explain why the green and yellow categories in “Table 3.2.P.2-3. Summary of Functional Relationships Identified in the Formulation and Manufacturing Process of the Tofacitinib MR 11 mg Tablets” are stated to have the same impact on the quality of the product.
2. Explain why the Certificate of Analysis (CoA) for the hydroxypropylcellulose specifies (b) (4) with specification for the (b) (4) of a range of (b) (4) cps when the statement is made on Page 27 of P.2.2 that the acceptable range of viscosity is (b) (4) cps.
3. Explain why the (b) (4) of hydroxypropyl cellulose and cellulose acetate are not included in the specifications in P.4.1 when these have been identified as critical material attributes in Section P.2.2.1 Page 28.
4. Amend the specifications for receipt of the (b) (4) (b) (4) to include a CoA from the supplier.
5. Provide a copy of the test procedures (IR and Appearance) for the (b) (4) (b) (4)

6. Explain why the acceptance criteria for the retention times in the following tests are broad:

Test Procedure	Acceptance criterion
6842A Identity and Purity	(b) (4) minutes
6843A Identity, Content Uniformity, and Assay	(b) (4) minutes
6844A Dissolution	minutes

7. Confirm the accuracy of the reported results for individual recoveries (Accuracy) in the Methods Validation reports for methods TM-01-6842A Identity and Purity and TM-01-6843A Identity, Assay, and content uniformity:

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

8. Provide an explanation for the source of (b) (4) leading to the formation of (b) (4)

9. Specify whether the caps are child-resistant.

10. Specify the tablet count for the first (b) (4) commercial scale batches of drug product to be placed on stability (section P.8.2)

11. Change the dosage form name in the label (b) (4) to Extended Release.

12. In your response to the FDA 483 Observation #1, you stated (b) (4)
(b) (4)

- a. (b) (4)

- b. Provide information on how (b) (4)

- c. Provide product batch data, preferably at the commercial scale, to demonstrate the (b) (4) is capable of producing the product with acceptable quality. The data should include batch size, number of (b) (4), number of tablets

manually inspected, the manual inspection/verification result of the drilled tablets accepted (b) (4) and the batch analysis data.

- d. Update the Section 3.2.P.3.3 and 3.2.P.3.4 in the NDA to include (b) (4)

13. In the amendment submitted on October 30, 2015, (b) (4) considered as a critical attribute as no impact on in-vitro dissolution performance was

(b) (4)

- a. Provide detailed development data (b) (4) to support the control limits (b) (4)

- b. Include the control limits (b) (4) in your commercial manufacturing batch record.

14. You have provided data on the (b) (4)

(b) (4)

(b) (4) However, the dissolution data provided in the amendment does not contain the individual dissolution data. On October 30, you submitted another amendment where (b) (4)

- a. During the process validation, make sure you test the validation batches for the entire (b) (4). The representative samples taken out from (b) (4) as well as dissolution.

- b. In addition, provide a revised sampling plan for (b) (4) be used for process validation and the commercial manufacturing.

15. You have provided the (b) (4) test results in Table 2 to Table 11 in your response to the Agency's comment 2 dated September 4, 2015. It is noticed that your sample size for (b) (4) testing is more than (b) (4)

(b) (4) Limit your sample size to not more than (b) (4) testing during your process validation.

16. You have provided a (b) (4) for Tofacitinib Citrate MR 11 mg (effective date 9/4/2014), and proposed a (b) (4) study on (b) (4) Clarify whether you plan to do the (b) (4) Also clarify whether (b) (4) content uniformity (b) (4)



18. In the response to Query 2b of the CMC information request (dated September 4, 2015), you stated that "Content uniformity (b) (4) as suggested by the Agency". However, it was not included in Section 3.2.P.3.4 in the amendment submitted on October 30. Please include the CU testing with (b) (4) as an in-process control testing in the Section 3.2.P.3.4 of the NDA.

19. Provide one table that lists all the in-process control and testing for process validation, and another table for commercial manufacturing. Also include the sample size and location, sampling frequency, number of samples tested for each of sampling locations, and acceptance criteria for each test in the tables.

20. Provide your IVIVC project file in Phoenix Wizard Platform (WinNonlin project file (*.phxproj)).

If you have any questions, please contact Giuseppe Randazzo, Office Director (Acting), Office of Programs and Regulatory Operations, serving as the Regulatory Business Process Manager (RBPM), at (301) 796-3277.

Sincerely,

Giuseppe
Randazzo -S

Digitally signed by Giuseppe Randazzo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300366672,
cn=Giuseppe Randazzo -S
Date: 2015.11.12 15:24:59 -05'00'

Giuseppe Randazzo, M.S.
Office Director (acting)
Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
Center for Drug Evaluation and Research



NDA 208246

INFORMATION REQUEST

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Gary F. Perry
Director, Worldwide Safety and Regulatory

Dear Mr. Perry:

Please refer to your New Drug Application (NDA) dated April 24, 2015, received April 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib (CP-690,550) Modified Release 11 mg Tablets.

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

1. Regarding Method TM-01-6842A: Explain why the acceptance criterion for Retention Time in the System Suitability Test is so broad (i.e. (b) (4) minutes.)
2. You provided summarized (b) (4) tablet content uniformity data in Tables 3.2.P.2.3-11 and 3.2.P.2.3-14.
 - a. Provide details regarding the nature of the batch, scale, manufacturing site, equipment train, process parameters, sampling location and frequency, number of samples tested for each location, mean, RSD, and individual test results;
 - b. Set the (b) (4) as an in-process testing, or provide justification for the lack of this control;
 - c. For commercial manufacturing, in addition to mean tablet weight, include a control for individual tablet weight, in the in-process control testing during the (b) (4)

3. You proposed [REDACTED] (b) (4) [REDACTED] (b) (4)
- Provide further information (including dissolution and [REDACTED] (b) (4) data) to justify in process control range proposed [REDACTED] (b) (4) %);
 - Additionally, provide the process parameters, the detailed dissolution data (mean and individual) at each time point and [REDACTED] (b) (4) listed in Table 3.2.P.2.3-18.
4. Clarify how the [REDACTED] (b) (4) will be identified during manufacturing and what procedures you will take to ensure [REDACTED] (b) (4) during and after your manufacturing process.
5. During the [REDACTED] (b) (4), coating parameters were studied as shown in Table 3.2.P.2.3-15 and Table 3.2.P.2.3-18. Even though all dissolution data passed the dissolution specification, [REDACTED] (b) (4). You also provided an example showing dissolution result for lot BSP 13097 that include [REDACTED] (b) (4) (Figure 3.2.P.2.3-4).
- Please clarify how the dissolution test was performed for the [REDACTED] (b) (4) and how the [REDACTED] (b) (4) was identified and when [REDACTED] (b) (4) during the dissolution testing;
 - Since the dissolution data for [REDACTED] (b) (4) was included in Figure 3.2.P.2.3-4, clarify whether you have conducted a systematic study with sufficient data to show the relationship between [REDACTED] (b) (4) and the dissolution performance;
 - Provide the process parameters for the coating, the detailed dissolution data (mean and individual) at each time point and [REDACTED] (b) (4) listed in Table 3.2.P.2.3-15;
 - Provide a summary table with detailed information for the statistically designed experiments including the lot number, the process parameters, the stress test results for [REDACTED] (b) (4) and the detailed dissolution results.
6. According to the study summary provided in Table 3.2.P.2.3-23, [REDACTED] (b) (4) [REDACTED] to the tablet dissolution. However, in your result summary (Table 3.2.P.2.3-24), you identified presence [REDACTED] (b) (4) as critical element as the [REDACTED] (b) (4) is required to achieve dissolution target, while [REDACTED] (b) (4) therefore, [REDACTED] (b) (4) dissolution relative to target.

- a. Clarify whether the dissolution profile is the same between (b) (4)
Please provide dissolution data for these (b) (4)
- b. (b) (4) should be controlled. Clarify how your manufacturing process controls (b) (4)
- c. Include an in-process control for the (b) (4)
7. In addition to the (b) (4) test results provided in the Table 3.2.P.2.3-25, provide detailed tablet dissolution data (all time points) to support your proposed (b) (4)
8. It appears numerous batches were manufactured, including development, registration and stability batches during the development phase. However, the scale for each batch is unclear. For example, for batch 13097 used for a clinical study, the size was stated to be around (b) (4) kg in Table 3.2.P.2.3-3 in Development report, but in the batch analysis, it was stated to be around (b) (4) kg.
- a. Provide a concise and clear summary table, or list of batches, including all the batch numbers, purpose, scale, manufacturing site, the formulation used for each batch (or the difference between the batches), equipment train, and key process parameters.
9. The dissolution specification at the 2.5 hour time point (b) (4) % (b) (4) based on the submitted data for your registration batches and the long term stability data. Based on the submitted dissolution data, we recommend the following dissolution acceptance criteria:
- 1 hour: NMT (b) (4) %
2.5 hours: (b) (4) %
6 hours: NLT (b) (4) %

Implement the recommended dissolution acceptance criteria for your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test.

If you have any questions, please contact Giuseppe Randazzo, Office Director (Acting), Office of Programs and Regulatory Operations, serving as the Regulatory Business Process Manager (RBPM), at (301) 796-3277.

Sincerely,

Giuseppe Randazzo
-S

Digitally signed by Giuseppe Randazzo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300366672,
cn=Giuseppe Randazzo -S
Date: 2015.08.06 17:24:31 -04'00'

Giuseppe Randazzo, M.S.
Office Director (acting)
Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
Center for Drug Evaluation and Research



NDA 208246

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Attention: Gary F. Perry, BS
Director, Worldwide Safety and Regulatory

Dear Mr. Perry:

Please refer to your New Drug Application (NDA) dated April 24, 2015, received on April 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Tofacitinib Modified Release (MR) Tablets, 11 mg.

We also refer to your amendments dated May 22, and June 15 and 19, 2015.

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 February 24, 2016.

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, mid-cycle, 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 January 27, 2016.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. We acknowledge our previous agreement with your proposed general plan of a pharmacokinetic (PK) development program to support filing of an NDA for the 11 mg daily, tofacitinib MR. However, upon further consideration, we are concerned that the differences in nominal dose between the already approved immediate release (IR) formulation (5 + 5 mg) and the proposed MR formulation (11 mg) are not consistent with the regulatory requirements for establishing bioequivalence. We refer you to 21 CFR 320.23. Specifically: *“Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.”* Thus, our expectation is that the MR and IR formulations would have equivalent bioavailability at the same molar/nominal dose.

In the absence of bioequivalence at the same molar/nominal dose, you would need to provide justification. The 21 CFR 320.23 continues, to state that, *“Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.”* If you plan to support your application using this provision of the regulations, you will have to provide an appropriate justification. The adequacy of this justification will be a review issue.

Clinical Pharmacology

2. We acknowledge that the proposed tofacitinib MR 11 mg QD appeared to exhibit comparable C_{max} and AUC relative to tofacitinib IR 5 mg BID. However, the C_{min} of tofacitinib MR 11 mg QD was about 30% lower than that observed with tofacitinib IR 5 mg BID. We also note that the overall tofacitinib concentration-time profile of tofacitinib MR 11 mg QD was not similar to that of tofacitinib IR 5 mg BID.
3. You have proposed [REDACTED] (b) (4)
[REDACTED] based on
similar simulated C_{max} and AUC values between [REDACTED] (b) (4) and IR 5 mg
QD. However, tofacitinib concentrations in the second day [REDACTED] (b) (4)
[REDACTED] than IR 5 mg QD regimen.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Biopharmaceutics

4. Provide the dissolution testing data for 12 units of your test product using the final QC method. Provide the summary data (mean, minimum, maximum and range) and individual raw data as well.
5. Provide the clinical and analytical sites associated with the IVIVC study (study # A3921195).

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.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult DIVISION NAME. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver for pediatric study requirement for this application for pediatric patients less than two years of age. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral for the pediatric study requirement for this application for pediatric patients 2 to 17 years of age. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

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

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/s/

SARAH K YIM
07/01/2015
Signing for Badrul Chowdhury, M.D., Ph.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208246

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pfizer Inc.
Eastern Point Road
Groton, CT 06340

ATTENTION: Gary F. Perry, BS
Director, Worldwide Safety and Regulatory

Dear Mr. Perry:

Please refer to your New Drug Application (NDA) dated and received April 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib (b) (4) Release Tablets, 11 mg.

We also refer to your correspondence, dated and received April 30, 2015, requesting review of your proposed proprietary name, Xeljanz XR.

We have completed our review of the proposed proprietary name, Xeljanz XR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 30, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

TODD D BRIDGES
06/25/2015

NDA 208246
Tofacitinib MR
Pfizer, Inc.

Dear Mr. Perry:

Your NDA 208246 submitted on Apr 24, 2015, is currently under review. We have the following comments and request for information:

1. Reference is made to summary of clinical pharmacology under Section 2.7.2. Under many figures and tables, you stated that the source data/analysis/report is “*available upon request*”. Provide data, model codes or control streams, and scripts used to generate the corresponding analyses, along with a brief description/report for every “available on request” statement in the summary of clinical pharmacology.

Submit data files as SAS transport files with *.xpt extension (eg. Data1.xpt) and other files should be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_R.txt).

2. Reference is made to Appendix 4 under Section 2.7.2. In the PreNDA meeting dated November 24, 2014, we recommended that you use all relevant data including different dosing regimens (QD and BID) for the PK/PD analysis. We also recommended PK/PD analysis for additional endpoints such as ACR20, ACR50, ACR70 to justify that the difference in the trough concentrations would not translate into difference in efficacy. In Appendix 4, you stated that “*Pooled data from four double-blind Phase 2 studies (A3921025, A3921035, A3921039, A3921040) comprising placebo and IR 1, 3, 5, 10 and 15 mg twice daily (BID) were utilized in the exposure-response (E-R) relationships.*”. Provide PK/PD analysis including the data from 20 mg QD in Study A391025 and update the summary report. Also, provide similar analysis and summary report for ACR20, ACR50, and ACR 70.

Provide data, model codes or control streams, and scripts used to generate the corresponding analyses for the updated PK/PD reports. Data files should be submitted as SAS transport files with *.xpt extension (eg. Data1.xpt) and other files be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt).

Submit the requested information to items listed under number 1 above via email to Sadaf.Nabavian@fda.hhs.gov by COB Friday, June 19, 2015, followed by an official submission to the NDA. Submit the requested information to items listed under number 2 above via email to Sadaf.Nabavian@fda.hhs.gov by COB Friday, July 31, 2015, followed by an official submission to the NDA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/6.10.2015

Cleared by: LJafari/6.10.2015

JChen/PJi/YWang/NNikolov/6.10.2015

Finalized by: SNabavian/6.10.2015

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/s/

SADAF NABAVIAN
06/10/2015



NDA 208246

NDA ACKNOWLEDGMENT

Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Gary F. Perry
Director, Worldwide Safety and Regulatory

Dear Mr. Perry:

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 (CP-690,550) Modified Release 11 mg Tablets

Date of Application: April 24, 2015

Date of Receipt: April 24, 2015

Our Reference Number: NDA 208246

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 June 23, 2015, 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

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

If you have any questions, call me at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN
05/06/2015



IND 117389

MEETING MINUTES

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

Attention: Jim T. Mayne, Ph.D.
Senior Director, Global Portfolio Lead

Dear Dr. Mayne:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tofacitinib Modified Release (MR) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 25, 2014. The purpose of the meeting was to discuss the format and presentation of the data in support of your future NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: November 24, 2014, 11:00-12:00 P.M. EST
Meeting Location: White Oak Building 22, Conference Room: 1421
Application Number: IND 117389
Product Name: Tofacitinib Modified Release (MR) Tablets
Indication: RA
Sponsor: Pfizer, Inc.

Meeting Chair: Badrul A. Chowdhury, MD, PhD
Meeting Recorder: Sadaf Nabavian, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Associate Director, DPARP
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, PhD, Clinical Reviewer, DPAPR
Lawrence Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Supervisor, DPARP
Satjit Brar, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology (OCP)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, OCP
Arthur Shaw, PhD, Product Quality Reviewer, OPS/ONDQA/DIVIII/Branch VIII
Teresa McMillan, PharmD, Safety Evaluator, Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)
Fang Wu, PhD, Staff Fellow, Office of Biopharmaceutical Sciences
Gregory Levin, PhD, Acting Team Leader, Office of Translational Sciences
Nyedra Booker, PharmD, MPH, Risk Management Analyst, OSE, Division of Risk Management (DRISK)
Sara Harris, PharmD, Safety Project Manager, OSE (on-call)
Jamie Wilkins Parker, PharmD, Team Leader, OSE, DRISK
Sadaf Nabavian, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Sriram Krishnaswami, PhD, Program Team Lead
Thomas C. Stock, DO, Clinical Team Lead

John Larmann, formulation development, CMC Lead
Manisha Lamba, MPharm, PhD, Clinical Pharmacology Lead
Donald E. Frazier, PhD, Safety Risk Lead
Douglas J. Ball, MS, Toxicology Lead
Rong (Ronnie) Wang, MPH, Statistics Lead
James Mayne, PhD, Global Regulatory Lead

1.0 BACKGROUND

Pfizer submitted a Type B Meeting Request to discuss the format and presentation of the data in support of their future NDA submission. The FDA's preliminary comments were sent to Pfizer on November 21, 2014. After review of these comments, Pfizer stated their intent to continue with the meeting as scheduled and requested to discuss the FDA's responses to Questions 1, 2, 4(a), and 6.

2. DISCUSSION

Question 1:

The planned NDA will be submitted in electronic Common Technical Document (eCTD) format in accordance with the International Conference on Harmonization (ICH) and FDA guidance on electronic submissions. A summary of the proposed eCTD format and outline of the Table of Contents (TOC) for the NDA application are provided in Appendix 1. Does the Agency concur with the format and placement of the information in the electronic submission for the planned NDA?

FDA Response:

Your proposed eCTD format appears reasonable. We note your proposal to provide a separate labeling for the tofacitinib modified release (MR) formulation which is consistent with the Agency's advice given in the pre-IND meeting written responses, dated March 22, 2013. However, the Agency has re-considered this recommendation and based on the available prior precedent of including different formulations in the same labeling, we recommend that you consider incorporating the MR information into the current labeling for the immediate release product.

Discussion:

The Sponsor sought clarification regarding Division's recommendations to incorporate the modified release (MR) labeling into the current labeling for the immediate release (IR) formulation. The Division reiterated that they would prefer that the Sponsor submits one label, combining both the IR and MR information. Further, the Division clarified that the Sponsor to submit the modified release formulation application as a stand-alone application rather than a supplement to the tofacitinib IR NDA. The Sponsor requested further clarification on how they should submit the label if they intend to also submit a new proprietary name. The Division of

Medication Error Prevention and Analysis replied that the submission of the proprietary name will be a review issue. The Division referred the Sponsor to the labeling of other products, such as Lescol (fluvastatin sodium) and Glucophage (metformin hydrochloride), as examples that contain both an immediate and extended release formulations in the same labeling.

The Sponsor indicated that they may have MR formulation for a number of different indications to what's on the current label for the IR formulation, and asked whether the Division had any concerns with that approach from the labeling perspective under a single label. The Division replied that the labeling should very clearly specify which indications align with which formulations under the appropriate section of the label.

Question 2

The Sponsor followed the Agency's recommendations from the Pre-IND meeting written responses (received 22 March 2013) and completed the following studies in the clinical pharmacology program to support potential registration of tofacitinib MR 11 mg formulation:

- a. Evaluation of single and multiple dose PK of the final MR 11 mg formulation compared to IR 5 mg BID formulation;***
- b. Evaluation of high fat meal on the final MR 11 mg formulation;***
- c. In-vitro in-vivo correlation (IVIVC) study with slow, fast, and target release rates of the MR 11 mg formulation;***
- d. An in-vitro evaluation of potential alcohol interaction.***

Does the Agency agree that data from these studies are adequate to support the NDA review?

FDA Response:

In general we agree that the clinical pharmacology studies are adequate to support the NDA submission. We have the following additional comments:

- a. We agree that the evaluation of single and multiple dose PK of the final MR 11 mg formulation compared to IR 5 mg BID formulation demonstrating the bioequivalence of tofacitinib exposure and Cmax for single and multiple dosing of MR 11 mg QD and IR 5 mg BID are adequate to support the NDA submission.*
- b. The in-vitro in-vivo correlation (IVIVC) study design seems adequate. We encourage you establish a level A instead of a level (b)(4) correlation for setting dissolution specifications for the new product and to pursue (b)(4) in the future. The acceptability of the IVIVC will be a review issue.*
- c. We acknowledge the in vitro study conducted to assess the potential for dose-dumping in the presence of alcohol. Include the result of this study in your NDA submission.*

In addition, submit a PK/PD analysis linking the systemic exposure of tofacitinib to efficacy using data from the previous studies in NDA203214. Specifically, identify the most relevant PK parameter (e.g. AUC, Cmax, or Cmin) for efficacy in order to appropriately bridge the IR efficacy information to the MR formulation.

Discussion:

The Sponsor sought further clarification and agreement regarding the submission of the PK/PD analysis and prior to the meeting provided the Division with additional details of their plans for further feedback during the meeting. The Sponsor proposed to use continuous DAS28 as a “reference” efficacy endpoint for PK/PD analysis to bridge between tofacitinib IR and MR and also proposed to cross-reference the data to the approved NDA 203214. The Division commented on the rationale to request PK/PD analysis in the NDA submission. As the Division noted differences in the trough concentration between the two formulations (lower for the MR), the Sponsor would need to provide adequate justification that such deviation will not affect the efficacy of tofacitinib in RA. For the PK/PD analysis approach, the Division accepted Sponsor’s proposal for DAS28, and suggested that the sponsor also explore other endpoints including ACR20, ACR50, and ACR70. As the sponsor proposed to cross-reference the analysis submitted in NDA 203214, the Division recommended that the Sponsor use all relevant data, including data obtained from different doses and dosing regimens (QD and BID) from the phase II studies, in their PK/PD analysis. The Sponsor acknowledged Division’s point and plan to provide justification.

A question was raised by the Sponsor on the specific PK parameters and the Division replied that it’s at the discretion of the Sponsor to use adequate PK parameters, with appropriate justification, to bridge the data for the IR to MR formulation.

The Division asked the Sponsor about their plans for the IR formulation once the new MR formulation gets approved. The Sponsor replied that they cannot provide a clear answer at this time given the complexity of the ongoing IR and MR formulation development program (b) (4).

(b) (4)

Question 3:

Does the Agency agree that presentation and discussion of data pertaining to these key biopharmaceutic aspects will be sufficient to support review? Pfizer would value feedback from the Agency on additional elements, if any, that are deemed necessary to support review of tofacitinib MR NDA.

FDA Response:

In addition to the data/studies you listed, we request that you provide the following biopharmaceutics information (not limited to) in your NDA submission.

- 1. Dissolution test:*** *Include the dissolution method report supporting the selection of the proposed test. Include the following information in the report:*

- a) *The pH solubility profile;*
 - b) *Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions used for each test. If possible, the dissolution profile should be complete and cover at least (b) (4) % release of the label amount or whenever a plateau (i.e., (b) (4)) is reached. We recommend use of at least (b) (4) per testing variable;*
 - c) *Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. Report the dissolution data as the amount of drug released with time;*
 - d) *Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g. drug substance particle size, drug substance solid state, hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.*
 - e) *Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.*
- 2. Dissolution acceptance criteria:** *Consider the following points for the selection of the dissolution acceptance criteria of your product:*
- a) *Use the dissolution profile data from the pivotal clinical batches for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*
 - b) *Establish specifications based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
 - c) *A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least (b) (4) % of drug has been released. If the*

maximum amount release is less than (b)₍₄₎%, the last time point should be the time when the plateau of the release profile has been reached.

Note that the final determination on the acceptability of the dissolution method is a review issue that may be determined during the IND or NDA. However, the acceptability of the proposed dissolution criteria for your product will be made during the NDA review based on the totality of the provided dissolution data.

- 3. *Extended Release Designation Claim:*** *Submit the following information to support the extended release designation claim (refer also to CFR 320.25f):*
- a) The BA profile established for the drug product rules out the occurrence of any dose dumping.*
 - b) The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved NDA.*
 - c) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.*
 - d) The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.*

Discussion:

No further discussion took place.

Question 4:

Does the Agency agree with the strategy for managing and presenting efficacy and safety data in the tofacitinib MR NDA? Specifically,

FDA Response:

The proposed strategy for managing and presenting the efficacy and safety data for the tofacitinib MR NDA submission appears reasonable.

Discussion:

No further discussion too place.

Question 4(a):

Pfizer proposes to provide a Summary of Clinical Efficacy (SCE) and a Summary of

Clinical Safety (SCS) and will not plan to include an Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) in the tofacitinib MR NDA. Does the Agency agree that this approach, and proposed content, is sufficient to support review of the tofacitinib MR NDA?

FDA Response:

The proposed strategy to provide a Summary of Clinical Efficacy and a Summary of Clinical Safety for the tofacitinib MR appears acceptable.

The integrated summary of efficacy (ISE) and integrated summary of safety (ISS) and detailed integrated analyses of all relevant data from clinical study reports are required by the regulations, and would be located in Module 5. However, if you believe section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and Module 5.

Discussion

The Sponsor sought additional clarification on Division's response related to SCE, SCS, ISE and ISS sections to ensure alignment and stated that they plan to cross-reference the relevant data from NDA 203214, to provide all the safety data from the bridging from the IR to MR program, and to also provide hyperlinks in the ISS and include table of contents. The Division stated that Sponsor's proposal was reasonable.

Question 4 (b):

Pfizer proposes to present safety data for the MR program in the SCS primarily by reference to the individual CSR for each study and does not plan to integrate safety and tolerability data from these seven healthy volunteer clinical pharmacology studies. Does the Agency agree with this approach?

FDA Response:

The proposed strategy to present safety data for the MR program in the Summary of Clinical Safety by reference to the individual CSR for each study appears reasonable.

Discussion:

No further discussion took place.

Question 5:

Does the Agency agree with the proposed safety data cut-off date and content for the 4 month safety update?

FDA Response:

We agree with your proposed safety data cut-off date and content for the 4-month safety update.

Discussion:

No further discussion took place.

Question 6:

Does the Agency agree with Pfizer's proposal to incorporate the tofacitinib MR formulation into the current Risk Evaluation and Mitigation Strategy (REMS) for NDA 203214/S-006 and that the present submission will include an Assessment Report (AR) of the current REMS program, along with the proposed modifications to the current REMS?

FDA Response:

We concur with your proposal to incorporate the tofacitinib MR formulation into the current Risk Evaluation and Mitigation Strategy (REMS) for NDA 203214/S-006. However, a complete review of the REMS, in conjunction with the final clinical review of the NDA will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

The Assessment Report (AR) that you propose to submit with the MR QD formulation NDA submission must address the following questions:

- 1. How does the benefit-risk profile change with the new formulation? What are the implications of this change for the current REMS (i.e., does this change indicate that the REMS would need to be modified)?*
 - Is the safety profile of the drug in the new formulation consistent with what is seen in the approved formulation?*
 - If the new formulation introduces new or worsened risks, can the risks be managed with the currently approved REMS?*
 - Is there new safety information to substantiate additional REMS elements, tools, or requirements? If so, how?*
- 2. Regarding your proposed REMS modification to reflect the addition of QD dosing posology information to the current Xeljanz REMS:*
 - Provide a brief overview of the impact of the REMS modification*
 - Will the modification introduce or alleviate burden to stakeholders? If so, how?*

- *Will the modification impact patient access? If so, how?*
 - *What additional evaluations are needed as part of the REMS assessment plan to assess the impact of the proposed modified REMS?*
3. *Has a full REMS assessment been done in the last 18 months prior to submission of the efficacy supplement for a new indication of use?*

If yes, at the time of that assessment was the REMS meeting its goals?

- *If the REMS was not meeting its goals at that time, were REMS modifications required or are there pending modifications to address the issues?*

Further Agency guidance regarding REMS modifications is forthcoming, and may be available prior to submission of your NDA.

Discussion:

The Sponsor sought clarification in how to go about consolidating the REMS for the modified release formulation into the existing REMS under the immediate release formulation. The Division of Risk Management (DRISK) referred the Sponsor back to the preliminary comments and reiterated that further guidance on REMS modifications will be forthcoming.

Question 7:

Does the Agency agree that the data cut-off for the information supplied in the AR can be up to 120 days prior to the submission date of the NDA?

FDA Response:

Your proposal is acceptable.

Discussion:

No further discussion took place.

3.0

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

*For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.*

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- *The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products*
- *Regulations and related guidance documents*
- *A sample tool illustrating the format for Highlights and Contents, and*
- *The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.*

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

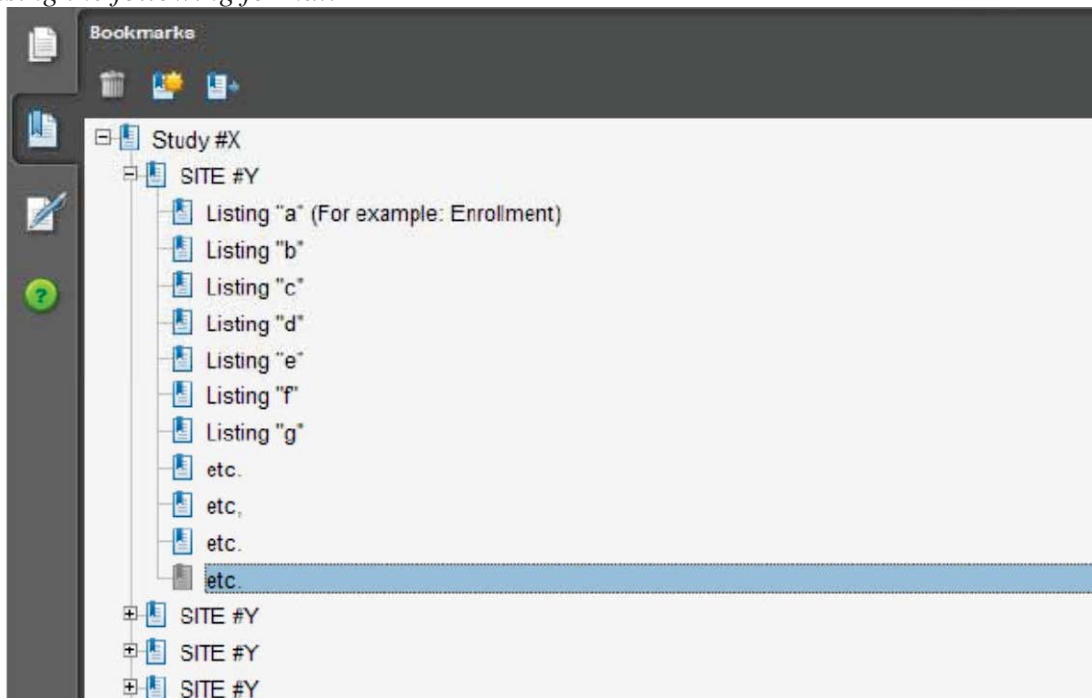
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

**Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

SADAF NABAVIAN
12/18/2014