APPLICATION NUMBER:

208246Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
1. Introduction

Pfizer submitted this 505(b)(1) New Drug Application (NDA 208,246) on April 24, 2015 seeking approval for the tofacitinib extended osmotic-release (XR) 11 mg once daily (QD) tablet formulation for the same indication for which the cross-referenced tofacitinib immediate release (IR) film-coated tablet has been approved under NDA 203,214 in November 2012 in the United States (US).

“Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). It may be given as monotherapy or in combination with MTX or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).”

In this NDA, the applicant proposes to rely on the findings of safety and efficacy from NDA 203,214 (Xeljanz IR formulation), based on (1) comparable exposure between the XR and IR formulations after single and multiple dose administration and (2) exposure-response relationships with tofacitinib from the IR formulation program, as advised by the Agency in pre-submission communications. Also, the applicant proposes to have both XR and IR formulations in the same labeling. Pfizer is the holder of both NDAs.
2. Background

Tofacitinib is an orally administered, selective, reversible inhibitor of the Janus kinase (JAK) family of kinases (JAK1, JAK2, JAK3 and Tyrosine Kinase 2 (TyK2)). JAKs are involved in myeloid and erythroid cellular development. They function by interrupting the signaling pathway from cytokine receptor to signal transducers and activators of transcription (STAT). Thus, tofacitinib inhibition of JAK activity decreases the cellular response to cytokines integral to lymphocyte activation, development, homeostasis, proliferation, and function.

Xeljanz (tofacitinib IR formulation) has been approved for marketing in the US since November 06, 2012 as a dose of 5 mg twice daily (BID) with efficacy claims including benefit in clinical response, i.e. signs and symptoms of the disease, improvement in physical function, inhibition of radiographic progression, and improvement in general health status in patients with moderate-to-severe RA. Xeljanz was approved with a boxed warning for serious infections, and lymphoma and other malignancies, and warnings for laboratory monitoring due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. A Risk Evaluation and Mitigation Strategy (REMS) was implemented to mitigate these risks. In addition, Pfizer is currently conducting a controlled clinical trial to evaluate the long term safety of Xeljanz doses in RA patients with a final study report expected in 2020.

The current NDA 208,246 is a 505(b)(1) application for Pfizer’s tofacitinib XR 11 mg QD tablet formulation. Extended release dosage form is defined as a dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or an immediate release dosage form.\(^1\)

Tofacitinib XR tablet formulation, an osmotic delivery tablet, uses extrudable core system (ECS) to extend the release of tofacitinib resulting in similar bioavailability (by Cmax and AUC\(_{24}\)) compared to tofacitinib IR 5 mg BID tablet formulation. The application is comprised of 7 phase 1 healthy volunteer (HV) studies (summarized in Error! Reference source not found.), conducted under IND 117,389, and designed to characterize the biopharmaceutical aspects of the XR formulation and establish similarity in key pharmacokinetic (PK) exposure parameters as compared to the currently approved tofacitinib IR 5 mg BID formulation after single and multiple dose administration. In addition, Pfizer submitted an exposure-response analysis for efficacy and safety from the tofacitinib IR formulation program to justify the relevance of the selected PK parameters for demonstrating similar exposure between the two formulations. Of note, the similarity in exposure is based on studies of a nominal daily dose of Xeljanz XR, 11 mg QD, which is different from the nominal daily dose of Xeljanz, 5 mg BID. However, since this is not a 505(b)(j) NDA, there is no statutory or regulatory requirement that bioequivalence must be established at the same molar dose of the active moiety.

This development program has been discussed and agreed upon with the applicant during pre-submission communications, to include: (1) an assessment of tofacitinib XR formulation in single and multiple-dose PK studies in healthy volunteers to characterize the biopharmaceutical aspects of the new formulation and to establish similarity in key PK exposure parameters for the XR formulation compared to the approved tofacitinib IR formulation, (2) an exposure-response analysis from the tofacitinib IR formulation program to justify the relevance of the clinical data from the IR formulation, and (3) incorporation of the XR information into the currently approved labeling for the IR formulation. Respectively, review of NDA 208,246, focused on these three aspects of the submission.

3. CMC/Biopharmaceutics

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>REVIEWER</th>
<th>BRANCH/DIVISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>N/A (reference to approved NDA 203,214)</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug Product</td>
<td>Art Shaw, PhD</td>
<td>NDPBIV/DNDPHI</td>
</tr>
<tr>
<td>Process and microbiology</td>
<td>Rose Xu, PhD</td>
<td>IABII/DIA</td>
</tr>
<tr>
<td>Facility</td>
<td>Yong Hu, PhD</td>
<td>PBAIV/DPAII</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Haritha Mandula, PhD</td>
<td>BB/DBII</td>
</tr>
<tr>
<td></td>
<td>Sandra Suarez, PhD</td>
<td>BB/DBIII</td>
</tr>
<tr>
<td>Regulatory Business Process</td>
<td>Giuseppe Randazzo</td>
<td>OPRO</td>
</tr>
<tr>
<td>Manager</td>
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<tr>
<td>Application Technical Lead</td>
<td>Craig M. Bertha</td>
<td>NDPBIV/DNDPHI</td>
</tr>
<tr>
<td>ORA Lead</td>
<td>Jose Melendez</td>
<td>ORA/SE-FO/SJN-DO/SJN-IB</td>
</tr>
<tr>
<td>Environmental Assessment (EA)</td>
<td>Craig M. Bertha</td>
<td>NDPBIV/DNDPHI</td>
</tr>
</tbody>
</table>

This section is largely excerpted/adapted from Dr. Bertha’s review.

Summary: The product quality and biopharmaceutics review teams have found no issues that would preclude approval of NDA 208,246. No CMC or biopharmaceutics Phase 4 commitments are recommended.

- General product quality considerations

1. Drug Substance

The drug substance product quality has been reviewed in detail under NDA 203,214. The drug substance tofacitinib citrate is a white to off-white Tofacinib citrate is highly soluble as per the Biopharmaceutics Classification System and the applicant indicates that it has low permeability (BCS class 3). The structure of tofacitinib citrate includes an arylamine function, which is a structural alert for mutagenicity. The drug substance is not photosensitive and the stability data provided supports both the proposed retest period of 18 months, as well as the post-approval stability protocol proposed. The applicant has followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the method that will be used for the determination of drug substance assay and impurities.
2. Drug Product

The tofacitinib extended release drug product is formulated using “extrudable core system” technology. The drug product contains the following excipients: sorbitol, hydroxyethyl cellulose, copovidone, Mg stearate, cellulose acetate, hydroxypropyl cellulose. The strength of the modified (extended) release tablet drug product is 11 mg of tofacitinib (as 17.8 mg of tofacitinib citrate).

The container closure system will be HDPE bottles with desiccant and heat induction closure liners. The drug product is provided as pink, extended release, film coated tablets with a drilled hole at one end of the tablet band and “JKI 11” printed on one side of the tablet.

The proposed expiry is 24 months, with storage at 20-25°C, which is acceptable.

- Facilities review/inspection

A pre-approval inspection has been performed at Pfizer’s drug product manufacturing site in Barceloneta, PR (FEI #2627208). Based on the firm’s response to the Form 483 observations, this facility is acceptable. The product quality team determined that based on the inspecational history, document review, and pre-approval inspecational coverage, there are no significant, outstanding manufacturing risks that prevent approval of this application and all of the manufacturing facilities are found to be acceptable.

- Other notable issues (resolved)

Because of negotiation between the biopharmaceutics team and the Applicant late in the review cycle, regarding the dissolution testing acceptance criteria, the process/facilities team required Pfizer to reassess the impact of the tightened dissolution criteria on the important process parameter acceptance ranges (PARs were set based partially on achieving dissolution, but relative to a more permissive set of acceptance criteria). As a result of these negotiations, the following dissolution method and dissolution acceptance criteria (based on in vitro-in vivo correlation, IVIVC, predictions) have been agreed upon with the Applicant:

Table 1. Dissolution Method and Dissolution Acceptance Criteria

<table>
<thead>
<tr>
<th>USP Apparatus</th>
<th>Spindle Rotation</th>
<th>Medium Volume</th>
<th>Temperature</th>
<th>Medium</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>II with Japanese sinkers</td>
<td>50 rpm</td>
<td>900 mL</td>
<td>37°C</td>
<td>0.05 M Potassium Phosphate Buffer, pH 6.8</td>
<td>1 hour: NMT (≥) 80% 2.5 hours: (≥) 80% 6 hours: NLT (≤) 80%</td>
</tr>
</tbody>
</table>

Source: FDA Product Quality Review, Biopharmaceutics Overall assessment
Based on the IVIVC analysis conducted internally, the difference in the predicted Cmax and AUC corresponding to the proposed lower and upper bounds in dissolution acceptance criteria meet the acceptability requirements, and the biopharmaceutics team has concluded that the PARs for the coating and other processes can remain as they are. I agree with this recommendation.

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: L. Steven Leshin, D.V.M, Ph.D.
Pharmacology/Toxicology Supervisor: Marcie Wood, Ph.D.

This section is largely excerpted/adapted from Dr. Leshin’s review.

Summary: There were no new nonclinical studies submitted in this application. All pharmacology and toxicology studies were previously reviewed under NDA 203,214. There are no novel excipients in the XR formulation. Two new degradant impurities, compounds (b) and (c), identified in the new XR formulation, were found to be of no toxicological concern. Drs. Leshin and Wood agree that there are no pharmacology/toxicology-related issues with NDA 208,246 that would preclude approval.

- Notable issues (resolved or outstanding)

With the exception of two degradants, compound (b) and (c), the impurities and degradants in the XR formulation were previously described and found acceptable, as reviewed in NDA 203,214. Compound (b) was detected in studies but had no structural mutagenic alerts and is acceptably controlled as an unspecified degradant of no more than (b)%. Compound (c) is the compound the applicant proposes to control as an unspecified degradant at no more than (c)% which is acceptable from pharmacology/toxicology perspective.

5. Clinical Pharmacology

Primary Clinical Pharmacology Reviewer: Jianneng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader: Ping Ji, Ph.D.
Pharmacometrics Team Leader: Yaning Wang, Ph.D.

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This section is excerpted/adapted from Dr. Jianmeng Chen’s review.

Summary: The clinical pharmacology and pharmacometrics review teams have found no issues that would preclude approval of NDA 208,246. The pertinent revisions to the proposed labeling recommended by the clinical pharmacology team have been agreed upon with the Applicant, as discussed in Section 12 in this document. No Phase 4 commitments are recommended by the clinical pharmacology team.

Table 2. Summary of PK parameters for tofacitinib IR and XR formulations

<table>
<thead>
<tr>
<th>Tofacitinib</th>
<th>IR</th>
<th>XR (osmotic tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>74%</td>
<td>10% less relative to IR</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>&lt;1h</td>
<td>3-4h</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>3h</td>
<td>5-6h</td>
</tr>
<tr>
<td>Linear PK</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Food effect</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Accumulation</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Source: Adapted from Dr. Jianmeng Chen’s Clinical Pharmacology Review

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The clinical pharmacology program constituted the foundation of this application, consistent with the pre-submission communications between the FDA and the Applicant. Specifically, this application provides information on establishing equivalent exposure (C<sub>max</sub> and AUC) between the XR and IR formulations to justify reliance on the finding of safety and efficacy with the IR formulation without the need for a stand-alone clinical development with the XR formulation. In addition, the Applicant provided exposure-response analyses from the IR formulation program in RA to justify the relevance of the selected clinical pharmacology parameters for PK equivalence.

The application consists of 7 PK studies in healthy adult subjects summarized in Table 3. These studies evaluated the following:
- Feasibility of administering tofacitinib as an XR formulation (Study A3921113);
- PK of pilot tofacitinib XR formulations (Studies A3921131 and A3921132);
- Single dose PK and relative bioavailability (BA) of tofacitinib XR 11 mg tablets from an initial commercial-level scale manufacture, compared to IR 2x5 mg tablets (Study A3921163);
- Effect of a high fat meal on the PK and BA of proposed-commercial tablet formulation of tofacitinib XR 11 mg (Study A3921180);
- Single and multiple dose PK and relative BA of the proposed-commercial tablet formulation of tofacitinib XR 11 mg QD relative to IR 5 mg BID (Study A3921212);
• Correlation of in-vitro dissolution with in-vivo plasma drug concentrations of XR tablet formulations with varying release rates (Study A3921195).

### Table 3. Key Design Features of the Clinical Studies Supporting the Application

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Objectives</th>
<th>Treatment Groups</th>
<th># of Subjects</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3921113 (Singapore)</td>
<td>Feasibility study of XR formulation</td>
<td>Single dose IR 10mg&lt;br&gt;20mg (capsule – 20mg (capsule – &lt;br&gt;20mg (capsule – ))</td>
<td>12</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921131 (Singapore)</td>
<td>Preliminary relative bioavailability of pilot formulations and food effect</td>
<td>Single dose IR 10mg&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted and fed&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted and fed</td>
<td>30</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921132 (Singapore)</td>
<td>Dose proportionality</td>
<td>Single Dose&lt;br&gt;XR 22mg (ECS osmotic tablet); fasted&lt;br&gt;XR 11mg (ECS osmotic tablet); fasted</td>
<td>20</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921163 (Belgium)</td>
<td>Relative BA of initial commercial-scale (osmotic) formulation</td>
<td>IR 10mg, fasted&lt;br&gt;XR 11mg (ECS osmotic tablet); fasted</td>
<td>26</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921180 (United States)</td>
<td>Food Effect on proposed-commercial (Osmotic) formulation</td>
<td>XR 11mg (ECS osmotic tablet); fasted and fed</td>
<td>24</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921195 (Belgium)</td>
<td>In-vitro dissolution with in-vivo plasma drug concentrations (IVIVC study)</td>
<td>IR 5mg, fasted&lt;br&gt;XR 22mg fasted&lt;br&gt;XR 11 mg (ECS osmotic tablet); fasted; 3 formulations – target release, slow release and fast release</td>
<td>36</td>
<td>Single Dose</td>
</tr>
<tr>
<td>A3921212 (Belgium)</td>
<td>Bioequivalence of proposed-commercial (Osmotic) formulation</td>
<td>Single dose phase: single dose IR 5mg BID&lt;br&gt;XR 11mg QD&lt;br&gt;Multiple Dose Phase&lt;br&gt;IR 5mg BID&lt;br&gt;XR 11mg QD (ECS osmotic tablet)</td>
<td>24</td>
<td>Single dose phase/Multiple dose phase (5 days)</td>
</tr>
</tbody>
</table>

Source: Adapted from Dr. Juwaria Wahed’s Clinical Review

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**ECS**: extrudable core system
**XR 22 mg ECS osmotic tablet**: XR 22 mg ECS osmotic tablet
**XR 22 mg**: XR 22 mg table
**XR 22 mg tablet**: XR 22 mg tablet

**IVIVC**: In vitro/in vivo correlation: A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed.
The pivotal study demonstrating the equivalent exposure of the to-be-marketed tofacitinib XR to the already approved IR formulation was Study A3921212, a randomized, open-label, 2-period, 2-way crossover study to evaluate the PK, BA, and safety of the tofacitinib XR 11 mg proposed-commercial tablet formulation administered as a single dose on Day 1 followed by QD dosing on Days 3 through 7, relative to tofacitinib IR 10 mg administered as two 5 mg doses, approximately 12 hours apart, on Day 1 followed by tofacitinib IR 5 mg BID dosing (approximately 12 hours apart) from Days 3 through 7 in healthy subjects. In the single dose period, serial blood samples for PK testing were collected over 48 hours for the determination of tofacitinib concentrations in plasma. In the multiple dose period, serial blood samples for PK testing were collected predose, and at multiple time points up to 24 hours post dose.

**PK Results from Study A3921212**

Median plasma tofacitinib concentration-time profiles following single dose administration on Day 1 and multiple doses are presented in Figure 1 and Figure 2, respectively.

**Figure 1. Median Plasma Tofacitinib Concentration-Time Profiles Following a Single Oral Dose of Tofacitinib XR 11 mg and Two Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1 (Study A3921212)**

![Median Plasma Tofacitinib Concentration-Time Profiles](image)

*Source: Adapted from Dr. Jianmeng Chen’s Clinical Pharmacology Review
MR-same as XR (extended release), IR-immediate release
Results of the statistical analyses are summarized in Error! Reference source not found.. The 90% CIs for the ratio (XR/IR) of adjusted geometric means for AUC24 and Cmax values were within the pre-specified bioequivalence acceptance criteria (80% to 125%), both after a single and multiple dosing, demonstrating equivalence of tofacitinib total daily exposure for tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID. Following the second tofacitinib IR 5 mg dose at 12 hours, peak (evening) concentrations for the IR treatment (Cmax2) were approximately 20 to 30% lower than peak (Cmax1) after the morning dose and were reached more slowly, with median Tmax2 observed 1 to 2 hours post-evening dose (13 to 14 hours post-morning dose). The clinical pharmacology review team independent analyses were consistent with the Applicant’s analyses.
Table 4. Summary of PK of Tofacitinib XR 11mg QD compared to Tofacitinib IR 5mg BID Following Single Dose and Multiple Doses (Study A3921212)

<table>
<thead>
<tr>
<th>Parameter (Unit)</th>
<th>Adjusted Geometric Means</th>
<th>Ratio (Test/Reference) of Adjusted Geometric Means</th>
<th>90% CI for Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MR 11 mg QD (Test)</td>
<td>IR 5 mg BID (Reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Day 1 (Single Dose Phase)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{inf} (ug/hr/mL)</td>
<td>253.2</td>
<td>243.7</td>
<td>103.92</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>35.98</td>
<td>39.22</td>
<td>91.75</td>
</tr>
<tr>
<td><strong>Day 5 (Multiple Dose Phase)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{24} (ug/hr/mL)</td>
<td>268.5</td>
<td>263.4</td>
<td>101.94</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>38.19</td>
<td>40.89</td>
<td>93.41</td>
</tr>
<tr>
<td>C_{min} (mg/mL)</td>
<td>1.044</td>
<td>1.478</td>
<td>70.64</td>
</tr>
<tr>
<td>C_{trough} (mg/mL)</td>
<td>1.820</td>
<td>2.475</td>
<td>73.54</td>
</tr>
</tbody>
</table>

a. The ratios (and 90% CIs) are expressed as percentages.

AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{24} = Area under the plasma concentration-time profile from time zero to 24 hours; C_{max} = maximum plasma concentration; C_{min} = Minimum plasma concentration; C_{trough} = Predose plasma concentration; CI = Confidence Interval; IR= Immediate Release; MR = Modified Release

Source: Adapted from Dr. Jianmeng Chen’s Clinical Pharmacology Review

MR-same as XR (extended release), IR-immediate release

Data from the other PK studies submitted in the application support the selection of the to-be-marketed formulation tested in the pivotal Study A3921212.

**Bioavailability Results, Fasted and Fed State**

Effect of a high fat meal on the PK and BA of proposed-commercial tablet formulation of tofacitinib XR 11 mg was assessed in Study A3921180. This was a phase 1, randomized, open label, single dose, 2-treatment, 2-period, 2-sequence crossover study to evaluate the effect of food on the PK of tofacitinib XR 11 mg proposed-commercial tablet formulation in healthy Western and Japanese subjects.

In the presence of food, absorption was slightly delayed. Following administration of a single tofacitinib XR 11 mg dose under fed and fasted conditions, total plasma tofacitinib exposure based on geometric mean AUC_{inf} was similar for both treatments as shown in Figure 3.
The clinical pharmacology review team concluded that the co-administration of the proposed-commercial tablet formulation of tofacitinib XR 11 mg with a high fat meal had no impact on the overall exposure of tofacitinib, and I agree.

*Exposure-Response Analyses for Efficacy*

The PK profile of the XR formulation, demonstrated overall similarity in PK parameters, with equivalent AUC and $C_{\text{max}}$, but 29% lower $C_{\text{min}}$ compared to the approved IR dosing regimen. To support the relevance of the selected PK parameters to demonstrated PK similarity between the two formulations, and a rationale that the observed lower $C_{\text{min}}$ with the XR formulation may not be clinically important to the efficacy of tofacitinib, Pfizer provided exposure-response information from the IR formulation program previously reviewed under NDA 203,214. This information was primarily derived from the dose-ranging study A3921025, a phase 2B double-blind study of placebo and 1, 3, 5, 10, 15 mg BID and 20 mg QD doses of tofacitinib IR. Following administration of the same total daily dose in two different regimens (i.e. IR 20 mg QD or IR 10 mg BID), $AUC_{24}$ was similar between the two regimens (within 10%), while $C_{\text{min}}$ was approximately 7-fold (86%) lower for the IR 20 mg QD dose. Despite a large difference in $C_{\text{min}}$, the efficacy (measured by American College of Rheumatology [ACR]20 response criteria at Week 12, as shown in Figure 4) of the IR 20 mg QD dose was similar to that of the IR 10 mg BID dose and consistent with the predicted BID dose response profiles across these endpoints. Similar results were observed for ACR50/70, and DAS28 measurements (data not shown).
Figure 4. Observed and Posterior Predicted Mean (10th-90th Percentile) Proportion of ACR20 Responders at Week 12 (Study A3921025)

Source: Adapted from Dr. Jianmeng Chen’s Clinical Pharmacology Review
Black solid line represents posterior mean model prediction, black dashed line represents 80% prediction intervals from the model; black filled squares represent observed data for BID doses; red filled square and blue filled circle represent 20 mg QD data placed either at a x-axis value of 20 (reflecting the same AUC24 as 10 mg BID) or at a x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg BID), respectively

In summary, the observed data and application of PK/PD modeling approaches consistently showed that C_{av} appears the most relevant parameter for efficacy and that the 29% lower C_{min} for the XR formulation may not be clinically important to the efficacy of tofacitinib. Similar clinical efficacy was observed with IR 20 mg QD dose compared to IR 10 mg BID despite a large difference in C_{min} (Error! Reference source not found.), and the improved goodness of fit characteristics with C_{av} compared to C_{max} or C_{min} support the conclusion that C_{av} is the most relevant PK parameter for efficacy.

Exposure-Response Analyses for Safety

All PK parameters for the tofacitinib XR 11 mg QD dose are equivalent (AUC and C_{max}) or slightly lower (29% lower C_{min}) as compared to those of the IR 5 mg BID dose. Of note, C_{min} for the XR formulation that did not exceed the C_{min} for the IR formulation was an intentional design component to help assure that there would be no additional safety risks associated with the XR formulation. For tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID in RA patients at steady state, both doses cover the in-vitro JAK1/3 IC50 of 17 ng/mL for approximately 12 to 13 hours over a 24-hour period (data not shown), indicating a similar level of enzyme inhibition over the dosing interval. To further support the argument that tofacitinib XR 11 mg QD dose would be expected to have similar safety profile to the already approved dosing of tofacitinib IR 5 mg BID dosing, Pfizer provided exposure-response analyses from the dose-ranging study A3921025 described above. For short term safety profile as measured by low density lipoproteins (LDL), high density lipoproteins (HDL), serum creatinine, hemoglobin and absolute neutrophil counts, the data from 20 mg IR QD in that study suggested that the
short term safety profile with daily sustained inhibition of JAK for 12-13 hours is comparable
to the inhibition of JAK under 10 mg BID dosing regimen (data not shown). For adverse
events of longer latency, such as serious infections and malignancy, the IR development
program in RA suggested that these were dose- and duration of exposure-dependent.
However, no specific tofacitinib concentration information provided additional explanation for
these AEs.

Based on these considerations, tofacitinib XR 11 mg QD dose would be expected to have
similar safety profile to the already approved dosing of tofacitinib IR 5 mg BID dosing.

- **Drug-drug Interactions (DDI)/Extrinsic Factors/Special Populations**

No specific studies were conducted to investigate the effect of DDI, intrinsic or extrinsic
factors on the disposition of tofacitinib XR. No formal special population studies were
conducted or submitted with the NDA. However, based on the similarity in exposure as
measured by Cmax and AUC, no significant differences are expected between the two
formulations with respect to DDI, intrinsic or extrinsic factors, and special populations.

In general, the aim of dose adjustment in special populations and DDIs is to produce a
comparable PK profile and a comparable range of relevant PK parameters as the general
population, to ensure the safety and efficacy of the drug in special populations. This may be
achieved by a reduced dose, a prolonged dose interval, or combination of both. The dosing
recommendation also considered the availability of different strength/ formulations, to make
the treatment available for special populations. Consistent with these considerations, Pfizer
proposed tofacitinib IR is currently approved as QD dosing regimen, as listed below:

- Patients with moderate to severe renal impairment
- Patients with moderate hepatic impairment (tocolitinib is not recommended for patients
  with severe hepatic impairment);
- Co-administration with potent inhibitors of cytochrome P450 (CYP3A4) (e.g.,
  ketoconazole, itraconazole) or;
- Co-administration with 1 or more medications that result in both moderate inhibition of
  CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

The clinical pharmacology review team recommended tofacitinib IR 5 mg QD for the above situations, and
I agree. Accordingly, the proposed labeling is revised to reflect these recommendations, as
detailed in Section Labeling below.
Thorough QT study or other QT assessment

No formal QTc study was performed for or submitted in NDA 208,246. However, QT effect was evaluated in a randomized, blinded, crossover, single-dose study, in which 60 healthy subjects received a supra-therapeutic tofacitinib dose of 100 mg (IR formulation), placebo, and moxifloxacin 400 mg reviewed under NDA 203,214. No significant QT prolongation effect was detected at the tested 100 mg tofacitinib dose. Based on the similarity in exposure as measured by Cmax and AUC, no QT prolongation is expected with the tofacitinib XR formulation.

Other notable issues (resolved or outstanding)

The Office of Clinical Pharmacology has determined the information in NDA 208,246 acceptable. No outstanding issues have been identified or Phase 4 commitments recommended.

6. Clinical Microbiology

Not Applicable.
7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Juwaria Waheed, M.D.

No efficacy studies were submitted in the NDA. This 505(b)(1) application relies on the Agency’s previous finding of efficacy for tofacitinib IR formulation. These data were reviewed under NDA 203,214, and included five phase 3, randomized, double blind, placebo-controlled trials, designed to assess clinical efficacy and safety of tofacitinib in the target population of adult patients with moderately-to-severely active established RA. The clinical program provided substantial evidence of improvement on signs and symptoms of RA, and improvement in physical function as measured by HAQ-DI. The applicant has subsequently provided substantial evidence of efficacy on radiographic outcomes with inhibition of radiographic progression. The data supporting the efficacy claims are reflected in the FDA-approved product labeling.

- Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL’s conclusions and ways that any disagreements were addressed.

Not applicable.

- Includes discussion of notable efficacy issues both resolved and outstanding

This application relies on Agency’s previous finding of efficacy for tofacitinib IR formulation, consistent with the pre-submission communications. This approach, while determined to be acceptable to support the efficacy of tofacitinib XR formulation, is predicated on (1) the adequate exposure-response information from the IR formulation program to justify the selection of pharmacokinetic parameters relevant to efficacy and (2) similarity in exposure between the two formulations for the selected parameters. These were adequately addressed by the Applicant as discussed in detail in Section 5 Clinical Pharmacology above.

8. Safety

- Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference

This 505(b)(1) application relies on the Agency’s previous finding of safety for tofacitinib IR formulation reviewed under NDA 203,214. The safety data from tofacitinib IR formulation RA development program identified the profile of a potent immunosuppressant, associated with inherent risks, such as serious infections, including opportunistic infections and tuberculosis. Tofacitinib administration was also associated with malignancy (excluding non-melanoma skin cancer) based on the increasing incidence rates in a dose-dependent manner and with prolonged duration of exposure, likely due to a dose- and time-dependent immunosuppression. Gastrointestinal perforations and interstitial lung disease were observed.
in the clinical trials, however the relative risk and role of tofacitinib treatment in the development of these adverse events is not well defined. Treatment with tofacitinib resulted in dose-dependent changes in laboratory parameters, such as sustained neutropenia and progressive lymphopenia, sustained elevations in total, LDL, and HDL cholesterol, small but significant elevations of mean serum creatinine, and liver enzymes elevations. While most of these were not associated with clinical adverse events in the controlled setting of the clinical trials, severe lymphopenia was associated with increased risk of infections.

Consequently, the US FDA-approved labeling for tofacitinib IR includes a boxed warning for serious infections and malignancies. The approval letter for tofacitinib IR (Nov 6, 2012) noted the aforementioned safety risks and required the applicant to conduct a postmarketing controlled active comparator study to evaluate the long term safety (safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy) of tofacitinib in patients with rheumatoid arthritis. This study is ongoing.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

The safety information in the NDA is derived from the PK studies in healthy subjects supporting the application as summarized in Table 3 above. These were Phase 1, open-label, randomized, crossover design studies where a total of 172 healthy subjects between 18 and 55 years of age, were administered tofacitinib (IR and/or XR) as single or multiple doses (up to 5 days). No adverse events of special interest, serious adverse events or deaths occurred in the 7 tofacitinib XR studies. One subject discontinued due to an adverse event, a superficial groin fungal skin infection, while receiving the tofacitinib IR 10 mg (5 mg BID) treatment in Study A3921212. The infections resolved after treatment with antifungals. There were no notable changes in vital signs, physical examination, or laboratory parameters. No new safety signals were identified. For additional details, refer to Section 7 in the clinical review by Dr. Juwaria Waheed.

- **Immunogenicity**—Not applicable.

- **Special safety concerns**—Not applicable.

- **Discussion of primary reviewer’s comments and conclusions**

Dr. Waheed has concluded that no new safety signals were identified in the tofacitinib XR clinical studies. I agree with Dr. Waheed’s conclusions.

- **Highlight differences between CDTL and review team with explanation for CDTL’s conclusion and ways that the disagreements were addressed**—Not applicable.

- **Discussion of notable safety issues (resolved or outstanding)**
This application relies on Agency’s previous finding of safety for tofacitinib IR formulation, consistent with pre-submission communications. This approach, while determined to be acceptable to support the safety of tofacitinib XR formulation, is predicated on (1) the adequate exposure-response information from the IR formulation program to justify the selection of pharmacokinetic parameters relevant to safety and (2) similarity in exposure between the two formulations for the selected parameters. These were adequately addressed by the Applicant as discussed in detail in Section 5 Clinical Pharmacology above.

9. Advisory Committee Meeting

Not applicable for this NDA. An Advisory Committee Meeting however, was convened for and discussed NDA 203,214 for tofacitinib IR formulation on May 09, 2012.

10. Pediatrics

- A brief documentation of the scientific data supporting extrapolation if extrapolation from one population to another is used to support efficacy.

Not applicable.

- Peds exclusivity board review - PPSR/WR—Not applicable.

- PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment

Tofacitinib XR represents a new dosage form and a new dosing regimen and approval of this NDA would trigger the requirements of the Pediatric Research Equity Act (PREA). With this submission, the applicant has requested a waiver of the requirements for pediatric assessment for children 0 to less than 2 years old, since polyarticular juvenile idiopathic arthritis (pJIA) is extremely rare in this age group and a deferral of studies for patients age 2-17 years old with pJIA until the completion of PREA requirements for tofacitinib IR formulation under NDA 203,214. The assessment of PK, efficacy and safety data from tofacitinib IR JIA program will determine the need for any pediatric studies with XR formulation. These requests have been included in the agreed initial Pediatric Study Plan (iPSP) on March 20, 2015. As part of this agreed iPSP, the applicant committed to pursue the development of an age-appropriate tofacitinib XR formulation to enable QD dosing in pediatric patients requiring doses lower than 11 mg and/or pediatric patients who are unwilling/unable to swallow the current XR 11 mg tablet. During the NDA review cycle, the applicant amended the iPSP with proposed studies and timelines for feasibility assessment and development of age-appropriate XR formulation.

The proposed pediatric study plan was discussed at the FDA Pediatric Review Committee (PeRC) on January 06, 2016 and while PeRC agreed with the overall proposal they recommended that the timelines for the development of the age-appropriate XR formulation be
shortened. To address PeRC’s recommendations, the applicant shortened the timelines for development of an age-appropriate XR formulation. The age-appropriate XR formulation development includes three studies which will be conducted as PREA post-marketing required (PMR) studies with the following timelines which are acceptable to the Division:

<table>
<thead>
<tr>
<th>Study</th>
<th>Final Protocol Submission</th>
<th>Study Completion</th>
<th>Final Report Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2016</td>
<td>April 2017</td>
<td>September 2017</td>
<td></td>
</tr>
<tr>
<td>March 2018</td>
<td>August 2018</td>
<td>January 2019</td>
<td></td>
</tr>
<tr>
<td>July 2019</td>
<td>December 2019</td>
<td>May 2020</td>
<td></td>
</tr>
</tbody>
</table>

- **Consults**—Not applicable.

### 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**

No issues were identified to trigger the AIP.

- **Exclusivity or patent issues of concern**

There are no exclusivity or patents issues of concern as the applicant, Pfizer, is the holder of both, tofacitinib IR formulation NDA 203,214, and the current tofacitinib XR formulation NDA 208,246.

- **Financial disclosures**—No issues.

- **Other GCP issues**—No issues.

- **OSI audits**

No application-specific inspections were conducted. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the clinical data without an on-site inspection. The analytical site, [redacted], has recently been inspected by OSIS and the nature of the findings from the inspection does not warrant inspection at this time. The clinical site, Pfizer Clinical Research Unit in Belgium, has recently been inspected by OSIS and the outcome from the inspection was classified as No Action Indicated (NAI).

- **Other discipline consults**—Not applicable.

- **Any other outstanding regulatory issues (resolved)**
As noted earlier in this document, tofacitinib XR has a nominal daily dose of 11 mg which is different from the nominal daily dose of the IR formulation, 10 mg (5 mg twice a day). Of note, this was intentional by design as approximately 10% of the dose is retained in the osmotic tablet.

The Agency has historically had differing approaches to bioequivalence of alternative formulations at different nominal doses. There are examples of applications that were:

- Approved with different nominal doses between immediate and extended release formulations, including based solely on bioequivalence studies. For example,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Extended Release/Alternative Formulation*</th>
<th>Immediate Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>ADHD</td>
<td>18 mg QD</td>
<td>5 mg TID</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Insomnia</td>
<td>12.5 mg QD</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>Pain relief</td>
<td>640 mg* TID/QID</td>
<td>800 mg TID</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Hyperlipidemia</td>
<td>145 mg* per day</td>
<td>200 mg per day</td>
</tr>
</tbody>
</table>

- Not approved because of different nominal doses. For example, NDA

Given the variability in the Agency’s historical approach to nominal dose, the Division convened an internal meeting on September 29, 2015 to discuss the legal and regulatory issues associated with this application, specifically the acceptability of an XR formulation of tofacitinib with a nominal dose of 11 mg once daily, different from the nominal dose of the IR formulation of tofacitinib (Xeljanz 5 mg twice daily, i.e. 10 mg total daily dose). This meeting included the NDA 208,246 review team and members of the Office of Regulatory Policy, the Office of Chief Counsel, the Office of Generic Drugs, the OND Immediate Office, and the Office of Drug Evaluation II. Meeting participants discussed the legal and regulatory precedents for approving a product with a different nominal dose, but that has equivalent AUC and Cmax to an approved product, and whether there were any existing legal or regulatory impediments to approving the application. After discussion at the meeting and confirmation with the Office of Chief Counsel, it was concluded that since Pfizer submitted NDA 208,246 for the XR tofacitinib product as a 505(b)(1) application, cross-referencing its own NDA 203,214 for the IR tofacitinib product, unlike for abbreviated NDAs, there is no statutory or regulatory requirement that a 505(b)(1) NDA establish bioequivalence at the same molar dose consistent with 21 CFR 320.23(b).

This issue was also discussed on November 13, 2015 at Office of New Drug Rounds with the CDER senior management. Similar discussion occurred, and the CDER management also agreed that from a scientific and policy perspective, matching exposures are relevant and
preferable despite the different nominal doses, and that having multiple nominal doses on the marketplace is acceptable.

Therefore, from a regulatory and policy perspective, the proposed XR tofacitinib product is acceptable, and there is no regulatory barrier to approving the XR formulation even though it has a different nominal dose as compared to the IR formulation.

12. Labeling

- **Proprietary name**

The applicant proposed the name “Xeljanz XR” for the extended release 11 mg tablets. This name was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) review team.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments**

None.

- **Physician labeling**

Major issues with the originally proposed labeling:

1) Boxed Warning: Delete the proposed addition of

2) Dosage and Administration and Use in Specific Populations: For:
   - Patients with moderate to severe renal impairment
   - Patients with moderate hepatic impairment (tofacitinib is not recommended for patients with severe hepatic impairment);
   - potent inhibitors of cytochrome P450 (CYP3A4) (e.g., ketoconazole); or;
   - 1 or more medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Delete the proposed recommendation. This is based on clinical pharmacology review team assessment that tofacitinib IR 5 mg QD provided a much better PK profile matching than in these populations.

3) Section 6 and 14: Delete the proposed text as this text is neither justified nor necessary. No new information form this application was included in either section 6 or 14.
4) Revise the reference to the new formulation to XR consistent with the product quality assessment of the product as an extended formulation.

- Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.

At this time of this review, the above issues have been resolved and agreed upon with the Applicant.

- Carton and immediate container labels (if problems are noted):

No problems noted.

- Patient labeling/Medication guide (if considered or required):

The review by Office of Prescription Drug Promotion (OPDP) did not identify issues. The review team Division of Medical Policy Programs (DMPP) recommended several formatting changes to the Medication Guide (MG) document with which I agree. The DMPP team also recommended deletion of XELJANZ XR throughout this MG for consistency with the PI and to help reduce patient confusion. However, I do not agree with this recommendation, as it may lead patients to believe that the safety information in the MG does not apply to XELJANZ XR when in fact, the safety concerns are the same with both formulations and must be conveyed to patients who take either Xeljanz or Xeljanz XR. The DMPP team agreed with my concerns and with keeping the reference to both XELJANZ and XELJANZ XR in the medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

NDA 208,246 provided adequate evidence that tofacitinib 11 mg XR tablets QD have equivalent AUC and Cmax to tofacitinib IR 5 mg tablets BID. Therefore, the Agency’s previous finding of safety and efficacy for tofacitinib IR 5 mg BID may be applied to tofacitinib 11 mg XR tablets given once a day. The review team has found no issues that would preclude approval of this NDA, and I concur. I recommend approval of the NDA, provided that agreement can be reached on revisions to the proposed label.

- Risk Benefit Assessment

The risk-benefit profile of tofacitinib 11 mg XR tablets QD is anticipated to be similar to the risk-benefit profile of tofacitinib IR 5 mg tablets BID, since the two products have equivalent AUC and Cmax.
The risk of having two products available with different nominal doses but similar exposures was assessed during review of this NDA (See Section 11, Other Regulatory Issues). If one medication is errantly substituted for the other, no safety concern would arise as the products have equivalent AUC and Cmax when taken as prescribed. The labeling and Medication Guide provide sufficient information to prescribers, patients, and caregivers to ensure appropriate dosing with either formulation. The slightly higher nominal daily dose (11 mg) of tofacitinib XR is unlikely to be confused with the IR formulation which utilizes a 5 mg pill. Further, the Agency’s experience with allowing both immediate and extended release formulations in a single label has not raised concerns with medication errors historically.

Therefore, overall, the risk:benefit profile of tofacitinib 11 mg XR tablets QD is acceptable.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

The NDA 203,214 for tofacitinib IR (Xeljanz) was approved on November 06, 2012 with a risk evaluation and mitigation strategy (REMS). In February 08, 2016, FDA released Xeljanz from its previously approved REMS (see February 08, 2016, letter, available at Drugs@FDA). The FDA has also determined that “maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1” (see February 11, 2015, letter, available at Drugs@FDA). There are no additional safety concerns with the XR formulation that would warrant a new REMS and the same considerations apply regarding maintaining the Medication Guide.

- **Recommendation for other Postmarketing Requirements and Commitments**

Three studies under PREA are recommended for the development of an age-appropriate formulation, as detailed in Section 10 above. No other postmarketing requirements or commitments are recommended by the review team.

- **Recommended Comments to Applicant**

None.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOLAY P NIKOLOV
02/21/2016