

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208246Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208246

Review 1

Drug Name/Dosage Form	Xeljanz® XR (tofacitinib) extended release tablets
Strength	11 mg
Route of Administration	Oral
Rx/OTC Dispensed	Yes
Applicant	Pfizer Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	24-FEB-2015	All
Amendment	22-MAY-2015	Drug product
Amendment	04-SEP-2015	Drug product, process, biopharm
Amendment	30-OCT-2015	Facilities
Amendment	25-NOV-2015	All
Amendment	11-DEC-2015	Drug product, process, facilities
Amendment	18-DEC-2015	Drug product
Amendment	23-DEC-2015	Drug Product
Amendment	22-JAN-2016	Drug product, process, biopharm
Amendment	05-FEB-2016	Drug product, process, biopharm
Amendment	10-FEB-2016	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A (reference to approved NDA 203214)	N/A
Drug Product	Art Shaw, PhD	NDPBIV/DNDPII
Process	Rose Xu, PhD	IABII/DIA
Microbiology	Rose Xu, PhD	IABII/DIA
Facility	Yong Hu, PhD	PBAIV/DPAII
Biopharmaceutics	Haritha Mandula, PhD Sandra Suarez, PhD	BB/DBII BB/DBIII
Regulatory Business Process Manager	Giuseppe Randazzo	OPRO
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII
Laboratory (OTR)	N/A	N/A
ORA Lead	Jose Melendez	ORA/SE-FO/SJN-DO/SJN-IB
Environmental Assessment (EA)	Craig M. Bertha	NDPBIV/DNDPII

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Type II: There was no DMF for the drug substance, tofacitinib citrate referenced in the application. All of the CMC information is referenced to the previously approved NDA 203214 for Xeljanz (tofacitinib) immediate release tablets.

Type III: No review was needed for the following Type III DMFs for packaging materials because sufficient information was provided in the application, per MaPP 5015.5

DMF	Item Referenced	Holder
		(b) (4)

Type IV: DMF (b) (4) from (b) (4) and the printing ink (b) (4) does not require review because the composition of the materials is provided in P.1.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	203214 (approved)	Xeljanz® (tofacitinib tablets), 5 mg for rheumatoid arthritis (RA)
IND		(b) (4)
IND		
IND	70903	Tofacitinib for RA (b) (4)
IND	117389	Tofacitinib for RA (ER tablets)
IND		(b) (4)
IND		
IND		

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			



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Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues – N/A
2. Action letter language, related to critical issues such as expiration date:

The action letter can include the 24 month expiration date that has been found to be acceptable for the drug product.

3. Benefit/Risk Considerations:

See the Risk Assessment III document for quality risk considerations; note that the biopharmaceutics team requested and received input from the clinical team regarding the drug product dissolution and their final recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – N/A

II. Summary of Quality Assessments

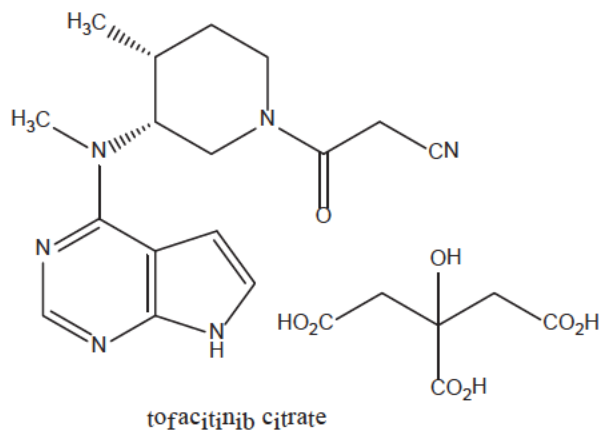
A. Drug Substance [tofacitinib] Quality Summary (reference to NDA 203214)

1. Chemical Name or IUPAC Name/Structure

3-((3*R*,4*R*)-4-methyl-3-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, 2-hydroxypropane-1,2,3-tricarboxylic acid

Molecular Formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ (citrate salt)

Molecular Weight: 504.50 g/mol (312.37 g/mole for free base)



2. Properties/CQAs Relevant to Drug Product Quality

The drug substance tofacitinib citrate (CP-690,550-10) is a white to off-white (b) (4) that is (b) (4)

Tofacitinib citrate is highly soluble as per the Biopharmaceutics Classification System and the applicant indicates that it has low permeability (BCS class III). 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 (b) (4) months, as well as the post-approval stability protocol proposed.

The applicant has also 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. These approaches included the use of risk-based assessment to identify drug substance quality attributes and process parameters that had potential to impact drug product safety and efficacy. Critical quality attributes (CQAs) of the drug substance were identified and process parameters were categorized as critical or non-critical (CPPs or NCPPs). The applicant performed multivariate experiments and modeled output data to establish links between synthesis process parameters and the quality attributes of intermediates and the final drug substance. In this way they defined the acceptance criteria for the material attributes of the synthesis materials (starting materials, reagents, etc.) and “operational boundaries” for process parameters, optimizing the process and providing greater assurance of the production of acceptable drug substance. In conjunction with these studies the applicant gained an understanding of the fate of and process parameters that affected the synthetic impurities in the drug substance. Overall, the applicant has presented additional information and data demonstrating enhanced process understanding of the drug substance synthesis process. In terms of the development of the assay and impurities method for the drug substance, the applicant has gone beyond the typical method validation studies (ICH Q2B) by defining an analytical target profile (ATP) for the method, performing risk assessment to determine which method parameters had high probability of impacting the method performance relative to the target profile, and performing multivariate experiments on these critical parameters to define the (b) (4)

The Agency is also still developing regulatory standards for using QbD approaches for analytical methods and is not taking any regulatory action with respect to the proposed ATP, which has been acknowledged by Pfizer.

3. List of starting materials

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(b) (4)

B. Drug Product [Established Name] Quality Summary**1. Strength**

The strength of the modified (extended) release tablet drug product is 11 mg of tofacitinib (as 17.8 mg of tofacitinib citrate).

2. Description/Commercial Image

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.

3. Summary of Product Design

The tofacitinib drug product is formulated using “extrudable core system” technology

(b) (4)

4. List of Excipients

The drug product contains the following excipients: sorbitol, hydroxyethyl cellulose, copovidone, Mg stearate, cellulose acetate, hydroxypropyl cellulose, (b) (4)

5. Process Selection (Unit Operations Summary)
 - a. Sterilization processes of the drug product, as applicable
 - b. Critical equipment

N/A

6. Container Closure

The container closure system will be HDPE bottles with desiccant and heat induction closure liners.

7. Expiration Date & Storage Conditions

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

8. List of co-packaged components

N/A

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xeljanz® XR
Non Proprietary Name of the Drug Product	Tofacitinib extended release tablet
Non Proprietary Name of the Drug Substance	Tofacitinib
Proposed Indication(s) including Intended Patient Population	Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate
Duration of Treatment	(b) (4)
Maximum Daily Dose	11 mg tofacitinib QD
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: The tofacitinib citrate solubility profile meets the high solubility criteria set forth based on the Biopharmaceutics Classification System (BCS) principles. Based upon the solubility and permeability data, in accordance with the Biopharmaceutics Classification System (BCS), the 11 mg dose of tofacitinib citrate is classified as BCS III (High Solubility-Low Permeability).
 - Drug Product: N/A
2. Biowaivers/Biostudies
 - Biowaiver Requests: None

- PK studies: N/A
- IVIVC: A3921195: A Phase 1, Randomized, Open-Label, Single Dose, Crossover Study to Investigate the Effect of Dissolution Rate on the Bioavailability of Modified Release Formulations of Tofacitinib in Healthy Volunteers

E. Novel Approaches – N/A

F. Any Special Product Quality Labeling Recommendations – N/A

G. Process/Facility Quality Summary



(b) (4)



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H. Life Cycle Knowledge Information (see separate Risk Assessment III)

**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE
SUMMARY**

Application Technical Lead Signature:

**Craig Bertha, CMC Lead for DPARP
DNDP/OPQ**

**Craig M.
Bertha -S**

Digitally signed by Craig M. Bertha
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13001
03470, cn=Craig M. Bertha -S
Date: 2016.02.10 12:21:16 -05'00'

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ASSESSMENT OF THE BIOPHARMACEUTICS

12. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The proposed MR formulation provides a QD dosing alternative to Xeljanz®, the currently approved tofacitinib immediate release (IR) tablet formulation administered 5 mg twice daily (BID), to enhance the ease of clinical use and patient convenience.

Dissolution Method Development:



(b) (4)

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Reviewer's Assessment:

- *The dissolution acceptance criteria were established based on clinical batch PSP13200, which was used in Pivotal BE study (A3921212), IVIVC study (A3921195) and Food Effect study (A3921180). Dissolution time points were selected that adequately characterize, and provide relevant information about the entire dissolution profile for this extended-release product: a time point in early stage to ensure that dose-dumping does not occur, a time point in the middle of*

the profile (approximately (b) (4) % dissolved) and a time point at a later stage to ensure complete release. Based on these criteria and the tofacitinib dissolution profile of the tofacitinib MR 11 mg tablets, the most appropriate time points are 1, 2.5 and 6 hours. The reviewer agrees with the applicant's approach for selecting a three-point specification.

- The Level A IVIVC model proposed by the Applicant does not justify a bioequivalent dissolution range of (b) (4) % drug dissolved and a target of (b) (4) % at the 2.5 hour time point of the mean dissolution profile, with NMT (b) (4) % dissolved at 1 hour and NLT (b) (4) % dissolved at 6 hours. Based on the data, the reviewer proposed the acceptance criteria of (b) (4) % at the 2.5 hr time point. Please refer to IVIVC review for additional comments and final decision about dissolution acceptance criteria.
- The Applicant stated that, "Some of the batch analysis results obtained throughout development of the tofacitinib MR tablets have been derived from analytical procedures that differ from the analytical procedures presented in this application for the evaluation of commercial drug product. This is due to the evolution of analytical methodology during the development process. Each procedure was validated at the time of its use. Some of the data presented in the tables were evaluated against specifications that differ from the proposed commercial specifications. Both the methods and specifications in place at the time of release for the respective products were appropriate for the stage of development and the intended use of the product". Hence these batches were not considered for setting of dissolution specifications.

IVIVC

IVIVC Proposed Model

Dissolution and plasma tofacitinib concentration-time profiles were used to attempt to build an in vitro in vivo correlation (IVIVC) model for the proposed Tofacitinib modified release 11 mg tablets. Initially, three (3) MR 11 mg tablets (slow, target and fast release) were used to develop the IVIVC. The MR 22 mg tablet (target release) was used for external validation of the model (refer to Figure 11). A Level A correlation was attempted where each point of the in vitro dissolution-time profile was mapped to in vivo performance (e.g., the in vivo dissolution-time profile obtained from deconvolution analysis of the plasma concentration-time profile). To assess the validity of the IVIVC, the absolute mean prediction error for C_{max} and AUC_{inf} was calculated for each MR formulation. The Applicant considered the model validated as the internal prediction of the overall average absolute prediction error was ≤10% for C_{max} and AUC_{inf} of the MR

11 mg tablet formulations, and the absolute prediction error was $\leq 15\%$ for C_{max} and AUC_{inf} for each individual MR 11 mg tablet formulation used to develop the IVIVC (slow, target and fast release formulations). The model was also considered validated by external prediction as the absolute prediction error for the MR 22 mg tablet (validation) was $\leq 10\%$ for C_{max} and AUC_{inf} .

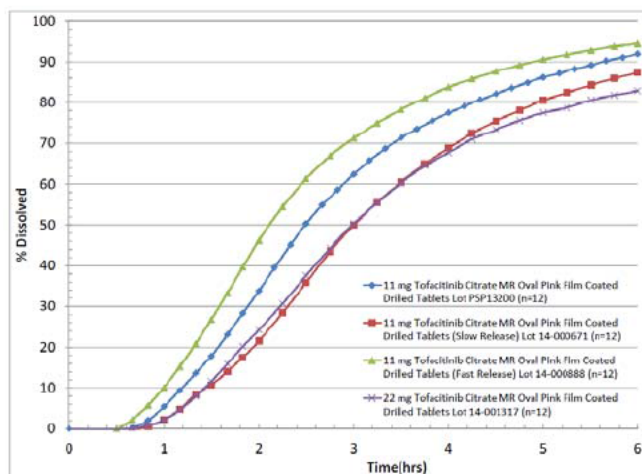
Dissolution Method used in the construction of the IVIVC for Tofacitinib MR Tablets

The dissolution method used in the construction of the IVIVC, and being proposed by the Applicant for quality control purposes for Tofacitinib[®] MR Tablets based on the in vitro performance of clinical batches and stability batches, is as follows:

Table 7: Dissolution test conditions

DISSOLUTION TEST CONDITIONS
1. Apparatus: USP apparatus II (Paddles) with Japanese Basket Sinkers
2. Dissolution Medium: 0.05 M Potassium phosphate buffer, pH 6.8
3. Volume: 900 mL
4. Temperature: 37 °C
5. Rotation Speed: 50 rpm

Figure 11 summarizes the dissolution profiles for the Formulations used in the construction of the IVIVC.



Source: ePharm Artifact ID 9527878.

Reviewer's Assessment:

- The reviewer calculated the f_2 values comparing slow and fast formulations to the target formulation (see Figure 1). The f_2 values are close to 50 (target vs fast f_2 : 58.41 and target vs slow f_2 : 56.83), showing that the dissolution profiles are

similar. The f_2 comparison of slow vs fast profile is less than 50 (fast vs slow f_2 : 42.30) showing that the dissolution profiles are different. Based on f_2 values, only slow and fast formulations were used to develop IVIVC. Initially, the reviewer used data only until the 6 hr time point since the target formulation had a dissolution profile generated only until the 6 hr time point; moreover, a plateau was reached with greater than 90% drug dissolved by 6 hours. After discussion with the Applicant regarding the procedures used to develop the IVIVC model, it was agreed to use the whole dissolution profile data, which includes dissolution data up to 12 hours.

In Vivo Study Used in the Construction of the IVIVC for Tofacitinib ER Tablets

Study A3921195

Study Title: A Phase 1, Randomized, Open-Label, Single Dose, Crossover Study to Investigate the Effect of Dissolution Rate on the Bioavailability of Modified Release Formulations of Tofacitinib in Healthy Volunteers.

Objectives:

Primary Objective

To estimate the relative bioavailability of the slow and fast release rate of the tofacitinib MR 11 milligrams (mg) formulations to the target release rate of the tofacitinib MR 11 mg formulation.

Secondary Objective

To evaluate the PK, safety and tolerability of single doses of the tofacitinib MR 11 mg and MR 22 mg formulations in healthy volunteers.

Exploratory Objective

To explore the in vitro-in vivo correlation (IVIVC) for MR 11 mg formulations of tofacitinib.

The study is designed as Phase I, randomized, open label, 5-treatment, 5-period, 6-sequence partial crossover study to investigate the relative bioavailability of MR formulations with differing release rates of tofacitinib when administered to healthy volunteers under fasting conditions.

Table 8: Formulations

Lot ID	11 mg Formulations			22 mg Formulation
	14-000802*	14-000888	14-000671	14-001317
Description	11 mg pink, film-coated tablets	11 mg pink, film-coated tablet, fast-release (b) (4)	11 mg pink, film-coated tablet, slow release	22 mg (b) (4)
Manufacturing Location	Barceloneta, PR	Barceloneta, PR	Barceloneta, PR	Sandwich, UK (b) (4)
Tofacitinib Citrate (mg)	17.771	17.771	17.771	
Sorbitol (mg)				
Hydroxyethyl Cellulose (mg)				
Copovidone (mg)				
Colloidal Silicon Dioxide (mg)				
Magnesium Stearate (mg)				
(b) (4)				
Manufacturing Location	Barceloneta, PR	Sandwich, UK	Sandwich, UK	Sandwich, UK (b) (4)
Cellulose Acetate (mg)				
(b) (4)				
Manufacturing Location	Barceloneta, PR	Sandwich, UK	Sandwich, UK	Sandwich, UK (b) (4)
(b) (4)				
Total (mg/tablet)				

Source: A3921195 IMPD.

* Lot 14-000802 corresponds to Barceloneta manufacturing lot ASP13200.

Table 9: Treatment Sequences:

Sequence (N = 36)	Period 1 (Fasted)	Washout	Period 2 (Fasted)	Washout	Period 3 (Fasted)	Washout	Period 4 (Fasted)	Washout	Period 5 (Fasted)
1 (n = 6)	A (MR 11 mg Target)	At least 72 hours	B (MR 11 mg Slow)	At least 72 hours	C (MR 11 mg Fast)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)
2 (n = 6)	A (MR 11 mg Target)	At least 72 hours	C (MR 11 mg Fast)	At least 72 hours	B (MR 11 mg Slow)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)
3 (n = 6)	B (MR 11 mg Slow)	At least 72 hours	A (MR 11 mg Target)	At least 72 hours	C (MR 11 mg Fast)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)
4 (n = 6)	B (MR 11 mg Slow)	At least 72 hours	C (MR 11 mg Fast)	At least 72 hours	A (MR 11 mg Target)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)
5 (n = 6)	C (MR 11 mg Fast)	At least 72 hours	A (MR 11 mg Target)	At least 72 hours	B (MR 11 mg Slow)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)
6 (n = 6)	C (MR 11 mg Fast)	At least 72 hours	B (MR 11 mg Slow)	At least 72 hours	A (MR 11 mg Target)	At least 72 hours	D (R 5 mg)	At least 24 hours	E (MR 22 mg Target)

Source: Section 16.1.1

A: Single oral dose of tofacitinib MR 11 mg (target release) tablet, administered as a 1 × MR 11 mg tablet, in a fasting state.

B: Single oral dose of tofacitinib MR 11 mg (slow release) tablet, administered as a 1 × MR 11 mg tablet, in a fasting state.

C: Single oral dose of tofacitinib MR 11 mg (fast release) tablet, administered as a 1 × MR 11 mg tablet, in a fasting state.

D: Single oral dose of tofacitinib IR 5 mg, administered as 1 × 5 mg tablet, in a fasting state.

E: Single oral dose of tofacitinib MR 22 mg (target release) tablet, administered as a 1 × MR 22 mg tablet, in a fasting state.

Abbreviations: IR = immediate release, mg = milligram(s), MR = modified release, N = total number of subjects to be enrolled the study, n = number of subjects to be randomized in each treatment sequence.

Figure 12: Pharmacokinetic Results:

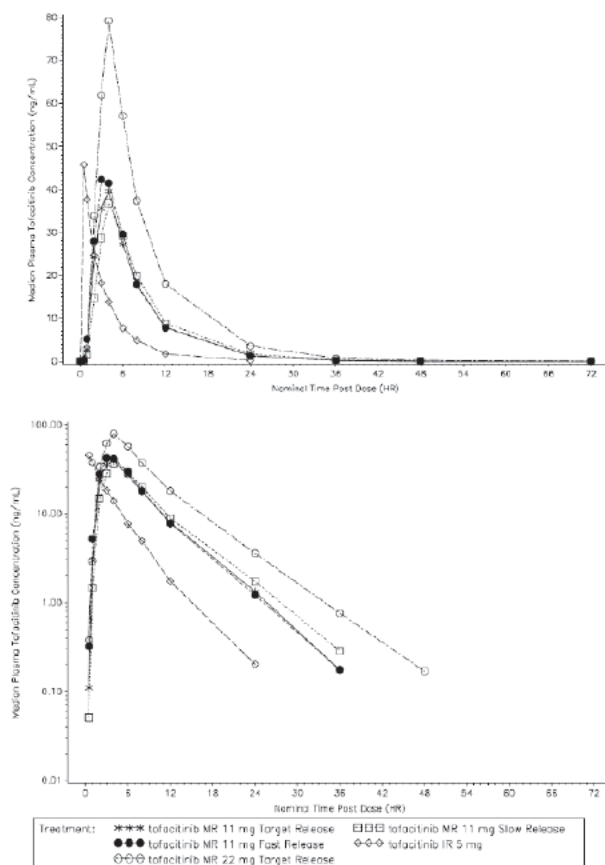


Table 10: Descriptive Summary of Plasma Tofacitinib PK Parameter Values

Parameter (unit)	Parameter Summary Statistics ^a by Tofacitinib Treatment				
	MR 11 mg Target Release	MR 11 mg Slow Release	MR 11 mg Fast Release	IR 5 mg	MR 22 mg Target Release
N, n	36, 36	36, 36	36, 36	36, 36	36, 36
AUC _{inf} (ng•hr/mL)	300.7 (27)	294.9 (25)	310.0 (27)	152.9 (24)	599.0 (25)
AUC _{last} (ng•hr/mL)	298.2 (27)	292.5 (25)	307.8 (27)	151.6 (24)	596.3 (25)
C _{max} (ng/mL)	41.40 (29)	37.23 (26)	44.83 (26)	48.14 (23)	76.47 (23)
T _{max} (hr)	4.00 (2.00, 4.00)	4.00 (3.00, 6.00)	3.00 (2.00, 6.00)	0.50 (0.50, 2.00)	4.00 (2.00, 6.07)
t _{1/2} (hr)	5.535 ± 2.740	5.869 ± 2.618	5.838 ± 2.914	3.322 ± 0.466	6.437 ± 2.798

Source: Table 14.4.3.1

The PK parameters are defined in Table 5.

Abbreviations: %CV = percent coefficient of variation, hr = hour(s), IR = immediate release, mg = milligram(s), mL = milliliter(s), MR = modified release, N = Number of subjects in the treatment group in the indicated population, n = number of subjects contributing to the summary statistics, ng = nanogram(s),

PK = pharmacokinetic(s), SD = standard deviation.

a Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t_{1/2}.

Table 11: Statistical Summary of Treatment Comparisons for Plasma Tofacitinib PK Parameters Following Single Oral Doses of 3 Different MR 11 mg Formulations

Parameter (unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio
	Test	Reference		
Slow Release Versus Target Release				
AUC _{inf} (ng•hr/mL)	294.9	300.7	98.07	94.44, 101.85
AUC _{last} (ng•hr/mL)	292.5	298.2	98.11	94.45, 101.90
C _{max} (ng/mL)	37.23	41.40	89.94	84.31, 95.94
Fast Release Versus Target Release				
AUC _{inf} (ng•hr/mL)	310.0	300.7	103.11	99.29, 107.08
AUC _{last} (ng•hr/mL)	307.8	298.2	103.23	99.39, 107.23
C _{max} (ng/mL)	44.83	41.40	108.30	101.52, 115.52

Source: Table 14.4.3.3.1

The PK parameters are defined in Table 5.

Abbreviations: CI = confidence interval, hr = hour(s), mg = milligram(s), mL = milliliter(s), MR = modified release, ng = nanogram(s), PK = pharmacokinetic(s).

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

Reviewer's Assessment:

- The reviewer agrees with the Applicant's study design.
- The relative bioavailability of the tofacitinib MR 11 mg slow and fast release rate formulations was 98.07% (94.44%, 101.85%) and 103.11% (99.29%, 107.08%), respectively, compared to the tofacitinib MR 11 mg target release rate formulation. The 90% CIs for the ratios were contained within the 80% to 125% equivalence limits.

Development of the IVIVC

In vitro data:

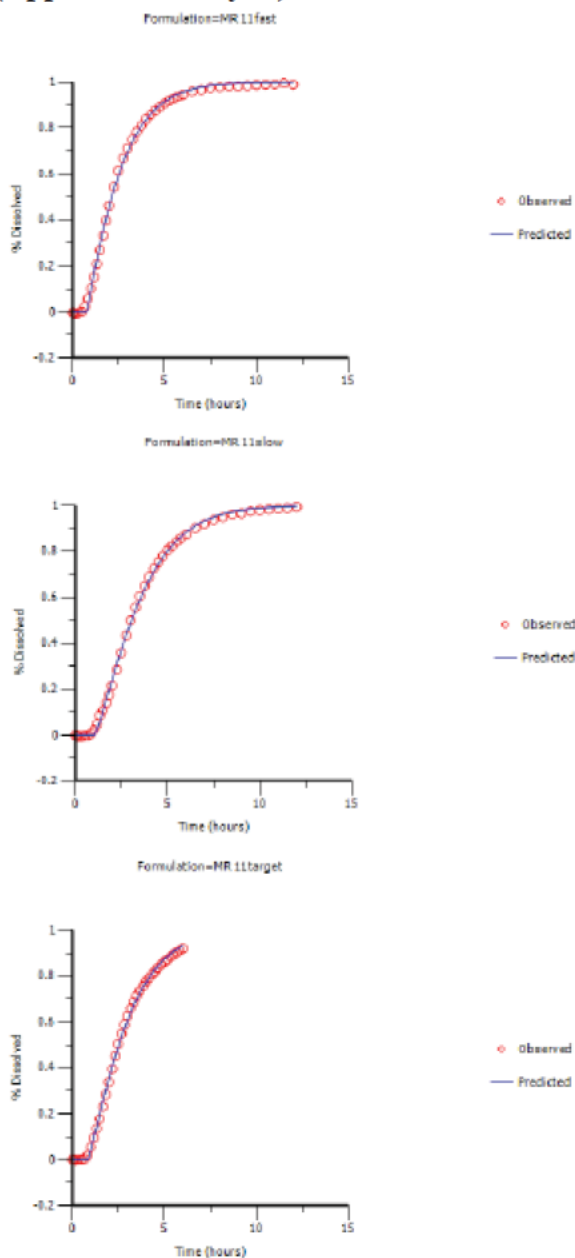
Dissolution testing was performed according to Method, TM100003327, which is the same as the quality control method used. This method utilizes United States Pharmacopeia (USP) Apparatus 2 (paddles) at 50 rpm in 0.9 L of pH 6.8 50 mM phosphate buffer at 37°C with Japanese sinkers. Through the use of an in situ ultraviolet (UV) fiber-optic assay system, tofacitinib dissolution data was obtained for a large number of time points over the course of the dissolution profile to provide good resolution of the in-vitro dissolution profile. The 2.5 hour time point was selected for differentiation of the fast and slow release dissolution profiles, as this time point for the target release formulation occurs when approximately 50% of the drug has dissolved and when the dissolution profiles for all three MR 11 mg formulations have high variability.

In vitro Dissolution Model Selection

In-vitro dissolution data generated with Method TM100003327 for the tofacitinib MR 11 mg and MR 22 mg tablets was evaluated in Study A3921195 using the Weibull equation. The applicant did not provide any rationale for selecting Weibull model.

The comparison between predicted dissolution profiles and observed dissolution results for MR 11 mg formulations (Slow: lot #14-000671, Fast: lot #14-000888, and Target: lot #PSP13200) and MR 22 mg formulation (lot #14-001317) are presented in the figure below and excellent agreement between predicted and observed values was obtained. The table below lists the regressed parameter values for flag, MDT, and int, as well as the goodness of fit, coefficient of determination (R^2), for each tofacitinib MR formulation. The in-vitro dissolution profiles were well-modeled by the Weibull equation.

Figure 13: Comparison between predicted dissolution profiles and observed dissolution results (Applicant's analysis).



Formulation=MR 22

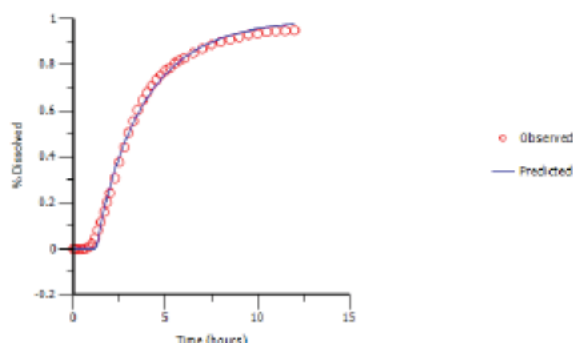


Table 12: Summary of Weibull Equation Parameters for Tofacitinib MR Dissolution Profiles (Applicant's analysis)

Dosage Form	F _∞	t _{1/2} (hours) ^a	MDT (hours) ^a	b ^a	int	R ²
MR 11 fast	1	0.75 (4.1%)	1.92 (2.2%)	1.13 (2.7%)	0	99.95%
MR 11 target	1	0.83 (5.2%)	2.30 (2.3%)	1.21 (2.9%)	0	99.93%
MR 11 slow	1	1.04 (4.5%)	2.70 (2.2%)	1.25 (2.9%)	0	99.95%
MR 22	1	1.24 (3.5%)	2.58 (2.7%)	0.93 (3.4%)	0	99.88%

Source: ePharm Artifact ID 9527919

a – data reported as: parameter value (CV%)

Reviewer's Assessment:

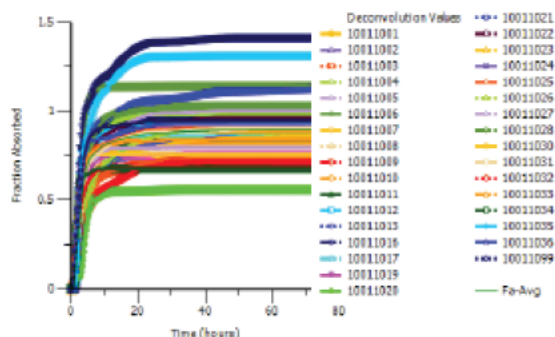
The reviewer used the same Weibull model to fit the in vitro dissolution data. The reviewer used other models and did not find any difference. Hence the Weibull model was found acceptable.

In-vivo absorption and deconvolution

The Figures below describe the individual cumulative fraction absorbed of the MR 11 mg target formulation (Lot: 14-000802), the MR 11 mg fast formulation (Lot: 14-000888), individual cumulative fraction absorbed of the MR 11 mg slow formulation (Lot: 14-000671), individual cumulative fraction absorbed of the MR 22 mg formulation (Lot: 14-001317).

Figure 14: Individual In-vivo Absorption Profiles for Tofacitinib MR 11 mg Tablets (Lot: 14-000802, Target batch) (Applicant's analysis)

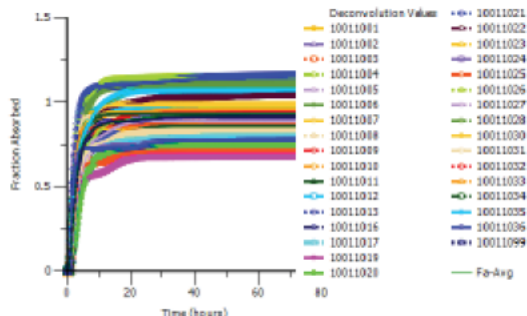
Formulation=MR L1target



Source: ePharm Artifact ID 9527919.

Figure 15: Individual In-vivo Absorption Profiles for Tofacitinib MR 11 mg (fast release) Tablets (Lot: 14-000888) (Applicant's analysis)

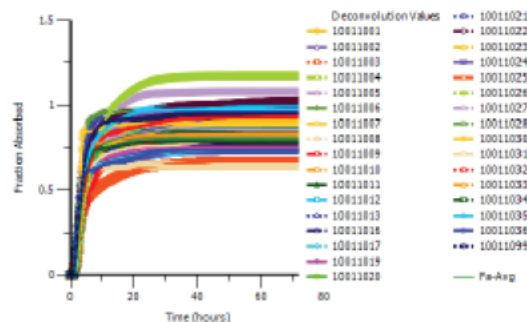
Formulation=MR L1fast



Source: ePharm Artifact ID 9527919.

Figure 16: Individual In-vivo Absorption Profiles for Tofacitinib MR 11 mg (slow release) Tablets (Lot: 14-000671) (Applicant's analysis)

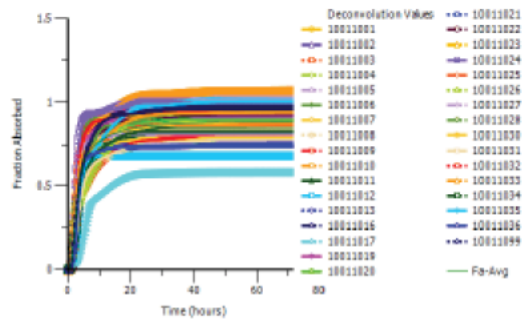
Formulation=MR L1slow



Source: ePharm Artifact ID 9527919.

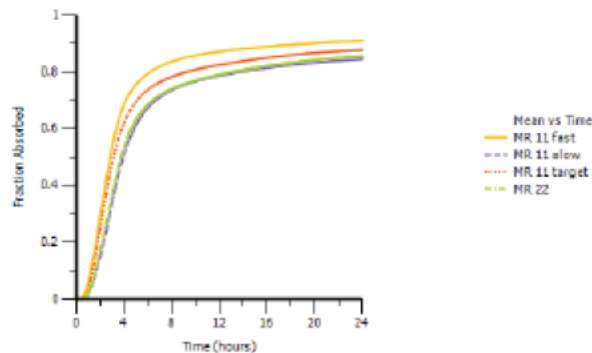
Figure 17: Individual In-vivo Absorption Profiles for Tofacitinib MR 22 mg Tablets (Lot: 14-001317) (Applicant's analysis)

Formulation=MR22



Source: ePharm Artifact ID 9527919.

Figure 18: Mean In-vivo Absorption Profiles for Tofacitinib MR 11 mg and MR 22 mg Tablets (Applicant's analysis)



Source: ePharm Artifact ID 9527919.

Reviewer's Assessment:

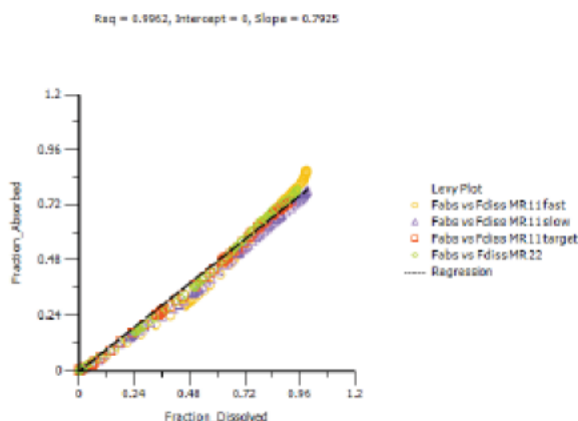
The Applicant stated that, "The individual plasma concentration-time data for Subjects 10011014, 10011015, 10011018, and 10011029 were averaged together to create a composite hypothetical individual (10011099) as a work around to a software operability issue". The total number of subjects used by the applicant was 37 including the hypothetical individual. The reviewer does not agree to the inclusion of this hypothetical individual. This hypothetical individual was deleted during the reviewer's analysis. Only 36 subjects (excluding the hypothetical individual) were considered during model building and validation.

IVIVC Correlation Development and Validation

A Levy plot presented in Figure 19 below was generated by using Phoenix WinNonlin to compare in-vivo absorption versus in-vitro dissolution data visually, as time-versus-time plots matched values for absorption and dissolution. The plot includes a linear fit of the

data points with intersection at origin, slope of 0.7925, and correlation line ($R^2 = 0.9962$).

Figure 19: In-vivo Absorption vs. In-vitro Dissolution (IVIVC) Relationship for Tofacitinib MR Tablets (Applicant's analysis)



Source: ePharm Artifact ID 9527919.

A five-parameter, user specified model, as described in the Table 13 was found to meet the internal and external predictability criteria outlined in the FDA-IVIVC guidance. The five parameters in the model described in the following Table are defined as follows: A1: absorption scaling factor (similar to “AbsScale” in WinNonLin user models); A2: time (in hours) at which drug absorption in-vivo transfers from the region of good absorption to the region of reduced absorption; A3: in-vitro time scaling factor for the region of reduced absorption; A4: in-vitro time scaling factor for the region of good absorption; Tcutoff: time (in hours) after which dissolution (“Diss”) should stop increasing. This model represents a linear, piecewise combination of the built-in WinNonLin model, $Fabs = AbsScale * Diss(Tscale * Tvivo)$ with Tcutoff, to account for the observation of two regions of absorption for tofacitinib from deconvolution analysis of the pilot bioavailability studies A3921113 and A3921131. The regressed values for each of the five parameters from the correlation development are listed in Table 14. The correlation provides an R^2 value for the MR 11 target, fast and slow release tablet data of 99.78%, 99.84% and 99.77%, respectively.

Table 13: User Specified Correlation Model for Tofacitinib MR Tablets (Applicant's analysis)



The correlation provides an R^2 value for the MR 11 target, fast and slow release tablet data of 99.78%, 99.84% and 99.77%, respectively.

Table 14: Summary of Regressed Parameter Values from the Proposed User Specified IVIVC Model (applicant's analysis)

Model Parameter	Value (CV%)	95% Confidence Intervals
A1	0.952 (0.07)	0.951 – 0.954
A2 (hours)	5.20 (0.56)	5.14 – 5.26
A3	0.116 (1.81)	0.112 – 0.120
A4	0.802 (0.30)	0.798 – 0.807
Tcutoff (hours)	24.9 (1.14)	24.4 – 25.5

Source: ePharm Artifact ID 9327919.

The user specified IVIVC model and corresponding model parameters predicted the C_{max} and AUC_{inf} to be within 10% of the observed values (see Table below) for both internal and external validation. For internal validation, the IVIVC predicted C_{max} and AUC_{inf} within 3.7% of the observed values. The average percent prediction error of less than 10% indicates that the correlation is predictive and meets the criteria set forth in the

FDA-IVIVC guidance. The low percent prediction errors for external validation (i.e., <10%) of the tofacitinib MR 22 mg tablets are summarized in Table 15.

Table 15: Validation of Tofacitinib MR Tablet Level A IVIVC Model (Applicant's analysis)

Formulation	AUC _{inf} (ng•mL/hr)			C _{max} (ng/mL)		
	Geo.Mean Observed	Geo.Mean Predicted	%PE	Geo.Mean Observed	Geo.Mean Predicted	%PE
MR 11 target (14-000802)	302.2	298.8	-1.1%	41.20	41.01	-0.5%
MR 11 fast (14-000888)	314.5	318.3	1.2%	45.55	43.87	-3.7%
MR 11 slow (14-000671)	295.3	301.4	2.0%	37.13	36.75	-1.0%
Average Absolute Internal %PE			1.5%			1.7%
MR 22 External (14-001317)	601.8	572.9	-4.8%	76.79	71.77	-6.5%

Source: aPharm Artifact ID 9327919.

Reviewer's Assessment:

- The reviewer does not agree with the Applicant's model due to the inclusion of a hypothetical individual as stated above.
- The reviewer used slow and fast profiles to build and validate the model internally and used the target profile as the external validator. MR 22 could not be used for external validation since the absolute prediction error for the MR 22 mg tablet (validation) was >10% for AUC_{inf} (Table 16).

Table 16: Validation results (reviewer's analysis):

Formulation	Parameter	Predicted	Observed	%PE	Ratio
MR 11 fast Internal	AUCINF_obs	315.9393	315.2102	0.231297	1.002313
MR 11 fast Internal	Cmax	44.13507	45.88199	-3.80741	0.961926
MR 11 slow Internal	AUCINF_obs	295.8625	294.9553	0.30757	1.003076
MR 11 slow Internal	Cmax	36.25648	37.08328	-2.2296	0.977704
MR 11 target External	AUCINF_obs	295.4413	301.8161	-2.11217	0.978878
MR 11 target External	Cmax	42.40444	41.1929	2.94115	1.029412
MR 22 External	AUCINF_obs	535.119	601.3563	-11.0147	0.889853
MR 22 External	Cmax	73.04224	77.13696	-5.30838	0.946916

Avg Internal	AUCINF_obs	305.7361	304.9146	0.269433	1.002694
Avg Internal	Cmax	40.00228	41.2487	3.018505	0.969783

- The reviewer used the same model as proposed by the Applicant and compared its robustness with other inbuilt models and found no significant difference. Hence the reviewer used the same model as the user defined model proposed by the Applicant.

Table 17: Validation Results excluding MR 22 as external validator (reviewer's analysis)

Formulation	Parameter	Predicted	Observed	%PE	Ratio
MR 11 fast Internal	AUCINF_obs	317.5393	315.2102	0.738889	1.007389
MR 11 fast Internal	Cmax	44.7059	45.88199	-2.5633	0.974367
MR 11 slow Internal	AUCINF_obs	299.3071	294.9553	1.475416	1.014754
MR 11 slow Internal	Cmax	34.69999	37.08328	-6.42686	0.935731
MR 11 target External	AUCINF_obs	291.8824	301.8161	-3.29132	0.967087
MR 11 target External	Cmax	42.91818	41.1929	4.188298	1.041883
Avg Internal	AUCINF_obs	308.2884	304.9146	1.107153	1.011065
Avg Internal	Cmax	39.38647	41.2487	4.49508	0.954854

Determining bioequivalent range for dissolution performance

Five individual tofacitinib MR dissolution profiles covering a range of 28% to 69% dissolved at the 2.5 hour time point (shown in Table below) were used by the Applicant as inputs into the Level A IVIVC model to generate in-vivo absorption profiles. The 2.5 hour time point was selected for differentiation of the various fast and slow release dissolution profiles, as this time point for the target release formulation occurs when approximately 50% of the drug has dissolved and when the dissolution profile has the greatest variability. These absorption profiles were then convoluted with the individual disposition pharmacokinetic parameters for tofacitinib to simulate mean plasma tofacitinib concentration-time profiles.

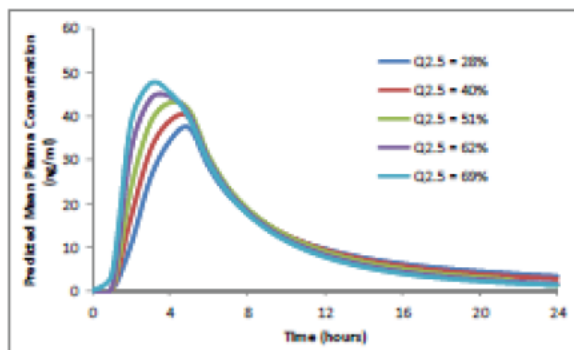
Table 18: Dissolution Profiles for Tofacitinib MR Tablets Used for Dissolution Specification Setting (Applicant's analysis)

Time (hours)	Q2.5 = 28% (-22%) ^a	Q2.5 = 40% (-10%) ^a	Q2.5 = 51% (+1%) ^a	Q2.5 = 62% (+12%) ^a	Q2.5 = 69% (+19%) ^a
0	-0.3	-0.3	0.1	-0.5	-0.2
0.5	-0.4	-0.8	0.1	-0.2	-0.3
1	1.5	3.2	5.1	8.5	12.3
1.5	8.4	12.1	16.3	23.2	32.9
2	17.1	24.1	33.2	45.7	54.6
2.5	27.8	39.8	50.5	62.2	69.2
3	42.4	52.6	64.1	72.6	77.8
3.5	54.4	63.2	72.9	78.9	82.7
4	64.0	72.6	79.4	84.0	87.4
4.5	71.8	79.4	84.3	86.8	91.0
5	77.3	83.2	87.9	90.3	93.0
5.5	82.2	86.4	90.5	92.7	95.1
6	85.4	89.4	93.4	94.7	95.8
7	90.2	93.6	---	96.8	97.7
8	92.8	96.1	---	98.1	99.1
9	95.7	97.6	---	98.3	99.3
10	97.1	98.1	---	99.6	99.5
11	98.4	98.8	---	99.7	100.3
12	99.1	100.2	---	99.5	100.0

Source: aPharm Artifact ID 9527874.

^a - Amount in parenthesis is the deviation from the target dissolution profile at 2.5 hours.

Figure 20: Simulated Plasma Tofacitinib Concentration-time Profiles (applicant's analysis)



Source: aPharm Artifact ID 9527874.

From these simulated profiles, C_{max} and AUC_{inf} values were determined and compared to the target data (i.e., MR 11 mg target release data from Study A3921195). These data are presented in the following table.

Reviewer's Assessment:

The reviewer does not agree with the prediction data set used by the Applicant to set the dissolution acceptance criteria. The reviewer used the proposed upper and lower dissolution bounds as it is the current practice.

Table 19: Prediction of Tofacitinib MR Tablets with Faster and Slower Release Profiles (Applicant's analysis)

Formulation	AUC _{inf} (ng ⁴ mL/hr)			C _{max} (ng/mL)		
	Target Geo.Mean	Predicted Geo.Mean	Ratio (Predicted/Target)	Target Geo.Mean	Predicted Geo.Mean	Ratio (Predicted/Target)
Q2.5 = 28% (-22%)*	302.2	294.7	0.975	41.20	34.01	0.825
Q2.5 = 40% (-10%)*	302.2	307.9	1.019	41.20	38.45	0.933
Q2.5 = 51% (+1%)*	302.2	304.9	1.009	41.20	42.55	1.033
Q2.5 = 62% (+12%)*	302.2	318.9	1.055	41.20	44.60	1.082
Q2.5 = 69% (+19%)*	302.2	322.3	1.068	41.20	47.21	1.146

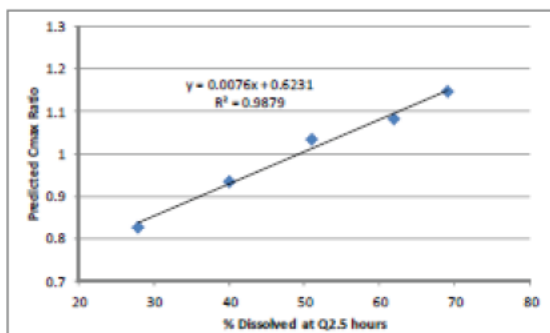
Source: ePharm Artifact ID 9327919.

* - Amount in parenthesis is the deviation from the target dissolution profile at 2.5 hours.

The Applicant stated that, "Changes in the in vitro dissolution performance are predicted to have a greater impact on the C_{max} ratio than the AUC_{inf} ratio, and, therefore, the bioequivalent range of dissolution performance will be limited by the impact on the C_{max} parameter. The C_{max} ratio values in Table above were then plotted in figure below and regressed to model the impact of the percent dissolved at the 2.5 hour time point on the predicted C_{max} ratio. If the (b) (4)

(b) (4) are considered in determining the range of C_{max} ratios that are bioequivalent, then the corresponding range in the mean C_{max} ratio that would meet bioequivalence would be (b) (4)%. This corresponds to a range of (b) (4)% ((b) (4)%) in the dissolution at the 2.5 hour time point (see table above). However, if the criteria for ensuring bioequivalence from the FDA IVIVC guidance is used (i.e., a 20% difference in C_{max} between the upper and lower dissolution specification limit), the corresponding dissolution range would be (b) (4)% (see table below). Both options provide an expansion of the dissolution specifications for tofacitinib MR tablets beyond the default range of +10%".

Figure 21: Impact of Percent Dissolved at Q2.5 Hours on the Predicted C_{max} Ratio (Applicant's analysis)



Source: ePharm Artifact ID 9527874.

Table 20: Impact of Dissolution Limits on Predicted Mean C_{max} Ratios, With and Without 90% Confidence Intervals (Applicant's analysis)

(b) (4)

Source: ePharm Artifact ID 9527874.

Reviewer's Assessment:

- The Applicant was informed through an Information Request (IR) and a subsequent T-con (held on January 12, 2016) about the unacceptability of the model due to the hypothetical individual used and the applicant agreed to modify the model excluding the subject. The Applicant was advised to build the model using slow and fast formulations and use the target formulation and MR 22 for external validation. The Applicant asked the Agency to provide their analysis, and the Agency's draft analysis was provided to the applicant in a CD.
- In a subsequent T-con held on January 19, 2016, the Applicant requested that the Agency use the entire dissolution profile up to 12 hours instead of the truncated dissolution profile up to 6 hours (which was previously used). Also, the Applicant requested the use of their predicted data set for PK predictions in place of proposed bound. The review team does not agree to that approach since changes on the release profile at specified time points may indicate changes on the mechanism of release, which has not been addressed as part of the model construction and validation. Secondly, The dissolution data presented in the pharmaceutical development report and manufacturing process development sections clearly show that changes in formulation/process variables have an impact on the whole dissolution profile and not only at the 2.5 hr time point.

- The review team does not agree with the Applicant's IVIVC model due to the reasons stated through the review:
 - Inclusion of the hypothetical individual in the analysis (10011099)
 - Dissolution profiles used in the analysis were almost similar with f2 comparisons greater than 50.
- The review team does not agree with the Applicant's approach of calculating half width confidence intervals. Based on the reviewer prediction of PK parameters using the $\pm 10\%$ variation of the target dissolution profile, the following PK predicted parameters (Cmax and AUCinf_obs) were observed as listed in Table 19.
- The reviewer re-ran the PK prediction using the reconstructed model (e.g. using (b) (4) hrs. dissolution data). This model does not support dissolution acceptance criteria beyond $\pm 10\%$ variation because the difference in predicted AUC between the slow and fast formulations is $> 20\%$ (please refer to the table below).

Table 21: Prediction of Tofacitinib MR Tablets with Faster and Slower Release Profiles (reviewer's analysis)

Formulation	Parameter	Predicted	Target	%PE	Ratio
Minus10	AUCINF_obs	254.6316	301.8162	-15.6336	0.843664
Minus10	Cmax	39.0523	41.1929	-5.19653	0.948035
Plus10	AUCINF_obs	333.9096	301.8162	10.63344	1.106334
Plus10	Cmax	44.67645	41.1929	8.456682	1.084567

This corresponds to a difference of 23.74% and 31.10% in AUC considering the lower and upper bounds, respectively. The difference in Cmax considering the lower and upper bounds is less than 20%. As AUC is the driving force for the safety and efficacy of this drug product and since the difference in predicted PK parameters is greater than 20%, acceptance criteria, a greater than $\pm 10\%$ variation when compared to the target profile is not supported by the level A correlation developed with the slow and fast formulations.

RECOMMENDED DISSOLUTION ACCEPTANCE CRITERIA

The Applicant proposed the following acceptance criteria based on the IVIVC model that they developed.



Reviewer's Assessment:

The original acceptance criteria proposed by the Applicant are as follows:

1 hour: NMT (b) (4) %

2.5 hours: (b) (4) %

6 hours: NLT (b) (4) %

The Applicant submitted an IVIVC model to support the wider acceptance criteria at the 2.5 hour time point. The reviewer reanalyzed the IVIVC data provided by the Applicant and finds that the proposed IVIVC model does not support a dissolution acceptance criteria beyond $\pm 10\%$ variation of the mean because the difference in predicted AUC between the slow and fast formulations is $>20\%$. Hence, a $\pm 10\%$ deviation at the 2.5 hour time point was proposed. The applicant was asked to acknowledge the acceptance of the following acceptance criteria based on their data:

1 hour: NMT (b) (4) %

2.5 hours: (b) (4) %

6 hours: NLT (b) (4) %

The applicant did not agree to FDA's proposed acceptance criteria and proposed the following revised acceptance criteria:

1 hour: NMT (b) (4) %

2.5 hours: (b) (4) %

6 hours: NLT (b) (4) %

The current practice for setting dissolution acceptance criteria in the presence of an IVIVC is based on meeting the criteria of NMT 20% difference in the predicted AUC and Cmax comparing the lower and upper bounds. Specifically, for this drug product the upper and lower bounds that should be input into the IVIVC model and which are reflective of the applicant's proposed acceptance criteria are:

Time point	Upper bound	Lower bound
1hr	(b) (4) %	(b) (4) %
2hrs	(b) (4) %	(b) (4) %
6hrs	(b) (4) %	(b) (4) %

It is noted that the dissolution profiles that the applicant used as input into the IVIVC and

being used to support the dissolution acceptance criteria are within but **NOT** at the edge of these bounds and are not representative of their proposal.

However, based on internal discussions with the Clinical and Clinical Pharmacology Divisions and taking into consideration the known exposure-response efficacy profile for the 3 mg IR tablet, the acceptance criteria listed below was then recommended. There is a concern for widening the upper bound acceptance criterion at the 2.5 hour time point beyond the (b) (4) used in the construction of the IVIVC and which was shown to be bioequivalent to the target batch. In addition, to ensure that the lower and upper bounds are BE at least to the target batch (clinical batch), the following acceptance criteria was conveyed to the Applicant on February 01, 2016, which included modification of the bounds at the 1 hour and 6 hour time points as follows:

1 hour: NMT (b) (4) %

2.5 hours: (b) (4) %

6 hours: NLT (b) (4) %

In a teleconference dated Feb 02, 2016, the Applicant agreed to the dissolution acceptance criteria at 2.5 hours and 6 hours, and counter-proposed an acceptance criterion of NMT (b) (4) % for the 1 hour time point. The Applicant stated that an acceptance criterion of NMT (b) (4) % at the 1 hour time point is restrictive. The Agency advised the Applicant to provide data and scientific justification to support the proposed acceptance criterion of NMT (b) (4) % for the 1 hour time point.

The Applicant provided the data for 10 batches manufactured at commercial scale on Feb 3, 2016, which show dissolution values with an average of 7.5% with a standard deviation (SD) of 1.35% at the 1 hour time point, with one validation/commercial batch showing dissolution results of 10%.

Batch	Batch No.	Dissolution at 1 hour (% release)
Registration	YSP13199	7
Registration	YSP13200	7
Registration	YSP13209	7
Development	YSP14103	8
Development	YSP14112	5
Clinical	YSP15247	7
Validation	M79458	9
Validation	M79459	7
Validation	M79460	10
Commercial	M82248	8

Note: Data for registration and development batches were based on N=18 for YSP13199 and N=12 for YSP13200 and 13209; The data for clinical batch was based on N=36; The data for validation and the first commercial batches were based on N=18. All dissolution test results were from (b) (4)

Considering the batch-to-batch variability at commercial scale, the dissolution acceptance criterion at 1 hour was set at (b) (4) % [i.e. (b) (4)]; thus a proposed value of NMT (b) (4) % is considered appropriate. The Applicant also provided supportive data generated using statistical Monte Carlo simulation technique to study the probability of passing USP <711> L1, L2 and L3 criteria per the proposed specification of NMT (b) (4) % at 1 hour (refer to the response to 02 Feb 2016 Teleconference Query, submitted 02/05/2016, Module 1: 1.11.1). Based on these simulations and the data presented in the table above, the Applicant is concerned that an acceptance criterion of NMT (b) (4) % at 1 hour leads to the potential to reject batches that are within routine batch-to-batch variability. A slight adjustment to NMT (b) (4) % at the 1 hour time point would ensure suitable overall drug release profile in concert with the agreed upon acceptance criteria at 2.5 hours and 6 hours without causing unnecessary rejects.

Reviewers Assessment:

The consideration of (b) (4) X SD is not a common FDA practice for setting the allowed variability in dissolution since acceptance criteria is not set based on process capability but clinical relevancy. Thus, the proposed upper and lower bounds in dissolution profiles were input into the IVIVC model to make predictions on Cmax and AUC. The difference in the PK predicted values for the lower and upper bounds in dissolution was less than 20%, which meets the criteria based on IVIVC.

CONCLUSION

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. The review team recommends

the following dissolution acceptance criteria for Tofacitinib MR Tablets, 11mg:

1 hour: NMT (b)(4)%

2.5 hours: (b)(4)%

6 hours: NLT (b)(4)%

The Applicant provided the revised specifications table with the updated acceptance criteria for the dissolution test on a submission dated 02/05/2015 (refer to Module 3: 3.2.P.5.1: Specifications and 3.2.P.5.6: Justification of Specifications).

13. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

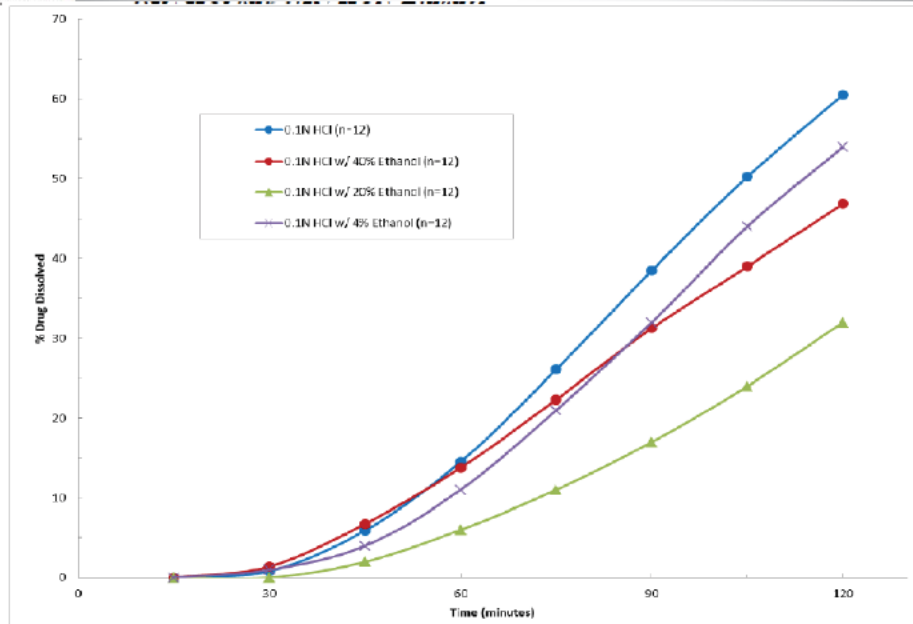
Reviewer's Assessment:

The Applicant has not proposed any changes in the formulation, manufacturing process or manufacturing sites during the development up until the commercial product. In addition, the Applicant has developed a validated IVIVC level A correlation which could be used to support future manufacturing site/formulation changes.

In Vitro Alcohol Dose Dumping Studies

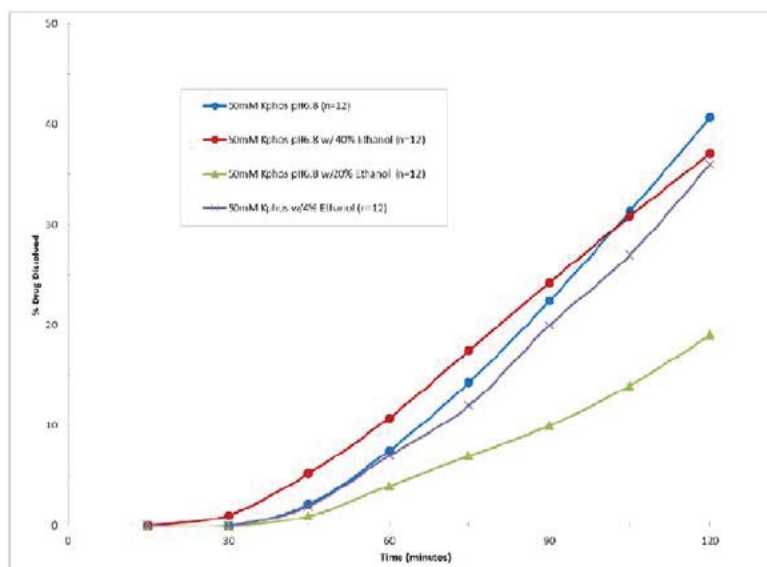
An in-vitro drug-alcohol interaction study was conducted for tofacitinib MR 11 mg tablets to evaluate the impact of ethanol on the in-vitro drug release of tofacitinib from the proposed commercial formulation. Eight dissolution media were prepared by mixing increasing ethanol concentrations (0%, 4%, 20%, and 40%) with the following two dissolution media: 1) SGF (Simulated Gastric Fluid) without enzyme (0.1N HCl), and 2) 0.05M potassium phosphate pH 6.8. The dissolution rates were tested at N=12 in each medium (See figures below). Dissolution samples were collected every 15 minutes for 2 hours and two additional samples were taken at 2.5 hours and 6 hours for comparative purposes.

Figure 22: Mean Drug Dissolved Profiles for Tofacitinib MR 11 mg Tablets in 0.1N HCl and 0.1N HCl / Ethanol



HCl=hydrochloric acid; N=normal; MR=modified release; n=number of replicates; w/=with.
Source: Module 3 (Section 3.2.P.2.2) Figure 3.2.P.2.2-21.

Figure 23: Mean Drug Dissolved Profiles for Tofacitinib MR 11 mg Tablets in Potassium Phosphate pH 6.8 Buffer and Potassium Phosphate pH 6.8 Buffer / Ethanol



Kphos=potassium phosphate; mM=millimolar; MR=modified release; n=number of replicates; w/=with.
Source: Module 3 (Section 3.2.P.2.2) Figure 3.2.P.2.2-22.

Reviewer's Assessment:

No in vitro dose dumping effect was observed with the varied concentrations of alcohol tested. No particular trend was observed with increased concentrations of alcohol. Though a reduction in dissolution was observed in 20% ethanol concentration, 40% ethanol concentration no further reduction was observed. The table below (table 4) shows f_2 calculations for various concentrations of alcohol used compared to 0% alcohol.

Table 22: F2 comparisons for different concentrations of alcohol

F2 comparisons	4%	20%	40%
0.1 N HCl	73.02	46.09	67.64
pH 6.8 buffer	86.4	57.33	82.75

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: ADEQUATE

The Applicant conducted a comprehensive dissolution method development to identify the appropriate dissolution apparatus, dissolution medium and volume, paddle rotation and speed. The applicant has conducted adequate method validation and the method is considered to be robust. The proposed dissolution method is discriminating and bio-predictive in terms of product and process changes. In vitro alcohol dose-dumping drug release studies were conducted using different media conditions and alcohol concentrations (0%, 5%, 20%, and 40% v/v ethanol). The results of these studies showed that the integrity of the MR formulation is not is compromised in the presence of alcohol.

Dissolution and plasma tofacitinib concentration-time profiles were used to build an IVIVC model for the proposed Tofacitinib MR 11 mg tablets. Two (2) MR 11 mg tablets (slow and fast release) were used to develop the IVIVC. The target 11 mg MR was used for external validation of the model. An immediate release tablet formulation of the drug product (5 mg) was used to determine the UIR. A Level A correlation was achieved where each point of the in vitro dissolution-time profile was mapped to in vivo performance. To assess the validity of the IVIVC, the absolute mean prediction error for C_{max} and AUC was calculated for each MR formulation. The model is considered validated since the internal prediction for the overall average absolute prediction error was $\leq 10\%$ for C_{max} and AUC of the MR 11 mg tablet formulations, and the absolute prediction error was $\leq 15\%$ for C_{max} and AUC for each individual MR 11 mg tablet formulation. The model is also considered validated by external prediction since the absolute prediction errors for the MR 11 mg (target release) was $\leq 10\%$ for C_{max} and

AUC. Therefore, the model is acceptable.

The following dissolution method and dissolution acceptance criteria (based on IVIVC predictions) have been agreed upon with the Applicant (refer to submission dated February 05, 2016):

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criteria
II with Japanese sinkers	50 rpm	900 mL	37°C	0.05 M Potassium Phosphate Buffer, pH 6.8	1 hour: NMT 13% 2.5 hours: 36-62% 6 hours: NLT 85%

Haritha Mandula, Ph.D. 02-08-2016
Primary Biopharmaceutics Reviewer
Division of Biopharmaceutics, ONDP/OPQ

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment, and I concur with the Reviewer's conclusion that the Biopharmaceutics information is adequate.

Kelly M. Kitchens, Ph.D.
Secondary Biopharmaceutics Reviewer
Division of Biopharmaceutics, ONDP/OPQ
February 9, 2016

I concur with the Biopharmaceutics Reviewers' analysis and conclusion.

Sandra Suarez Sharp, Ph.D.
Tertiary Biopharmaceutics Reviewer
Division of Biopharmaceutics, ONDP/OPQ
February 9, 2016

ASSESSMENT OF MICROBIOLOGY

14. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Microbial method has been established and validated for tofacitinib MR tablets, and is appropriate for the intended use. The firm proposed not to include microbial controls in the commercial specifications.

Reviewer's Assessment:

Tofacitinib MR tablet is a non-sterile solid oral dosage form. The (b) (4) (b) (4) % for the final release testing. During the stability study, (b) (4) and microbiological testing was conducted on the samples stored at 25°C/60% RH and 30°C/75% RH through 12 months and 40°C/75% RH through 6 months. (b) (4) (b) (4) but is still within the limit of (b) (4) %. Microbial test with bacteria, molds and yeasts were found to be within the limit according to USP <61> and USP <62> (b) (4) bacteria and (b) (4) molds and yeasts). The firm promised to continue the (b) (4) and Microbial limits test throughout the duration of the registration stability study.

Since the product is (b) (4). The risk associated with the microbial contamination is low as long as the (b) (4) is controlled within the limit of (b) (4) %. We agree that microbial controls do not need to be included in the commercial specifications based on the stability data on registration batches.

2.3.P.7 Container/Closure System

15. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

Refer to drug product review section.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

16. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Reviewer's Assessment:

Refer to drug product review section.

17. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:**Reviewer's Assessment:**

Refer to drug product review section.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**Reviewer's Assessment and Signature:**

Since the product is (b) (4) the risk associated with the microbial contamination is low as long as the (b) (4) is controlled within the limit of 0%. We agree that microbial controls do not need to be included in the commercial specifications based on the stability data on registration batches.

Rose Xu, Microbiologist 12/19/2015

Secondary Review Comments and Concurrence:

I concur with this assessment.

Chengjiu Hu, 12/30/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

18. Is the applicant's claim for categorical exclusion acceptable?

19. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment: Acceptable. Considering that the ER 11 mg tofacitinib tablet for QD use is an alternative to the approved IR 5 mg tofacitinib tablet for BID dosing, the applicant's claim for a categorical exclusion as per 21 CFR Part 25.15 (a),(d) is appropriate. Note that they also indicate that no extraordinary circumstances exist.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL**Reviewer's Assessment and Signature:**

Craig M. Bertha
25-JAN-2016

Secondary Review Comments and Concurrence:

Craig M. Bertha
25-JAN-2016

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1
Labeling & Package Insert**

For NDA only

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	XELJANZ XR ® (tofacitinib)	ACCEPTABLE
Dosage form, route of administration	extended release tablets, for oral use	ACCEPTABLE
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	XELJANZ XR Tablets: 11 mg	ACCEPTABLE

Conclusion: ACCEPTABLE

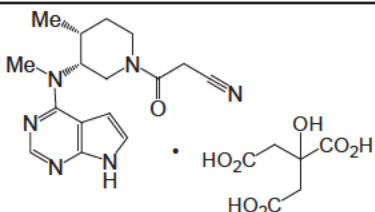
(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	tablets: extended release	ACCEPTABLE
Strengths: in metric system	11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate)	ACCEPTABLE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pink, oval, film-coated tablets with a drilled hole at one end of the tablet band and “JKI 11” printed on one side of the tablet.	ACCEPTABLE

Conclusion: ACCEPTABLE

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	XELJANZ XR (	ACCEPTABLE
Dosage form and route of administration	Tofacitinib	ACCEPTABLE
Active moiety expression of strength with equivalence statement for salt (if applicable)	11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate)	ACCEPTABLE
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose, HPMC 2910/Hypromellose, titanium dioxide, triacetin, and red iron oxide. Printing ink contains shellac glaze, ammonium hydroxide, propylene glycol, and ferrousferic oxide/black iron oxide.	ACCEPTABLE
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	JAK inhibitor	ACCEPTABLE
Chemical name, structural formula, molecular weight	 (3R,4R)-4-methyl-3-((methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-β-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base)	ACCEPTABLE
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: ACCEPTABLE

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) tablets	ACCEPTABLE
Available units (e.g., bottles of 100 tablets)	Bottles of 14 and 30	ACCEPTABLE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink, oval, extended release tablet with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet	ACCEPTABLE
Special handling (e.g., protect from light, do not freeze)	None	
Storage conditions		

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].	ACCEPTABLE

Conclusion: ACCEPTABLE

2. Container and Carton Labeling

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence)	Xeljanz® XR (tofacitinib)	ACCEPTABLE
Strength	11 mg	ACCEPTABLE
Route of administration	N/A	ACCEPTABLE
Net contents	14 tablets, 30 tablets	ACCEPTABLE
Name of all inactive ingredients	N/A	ACCEPTABLE
Lot number	Placeholder provided	ACCEPTABLE
Expiration date	Placeholder provided	ACCEPTABLE
"Rx only"	Present	ACCEPTABLE
Storage	N/A	ACCEPTABLE
NDC number	Provided	ACCEPTABLE
Bar Code	Placeholder provided	ACCEPTABLE
Name of manufacturer/distributor	Distributed by: Pfizer Labs Division of Pfizer Inc, NY, NY 10017 MADE IN IRELAND	ACCEPTABLE

Conclusion: ACCEPTABLE



**QUALITY ASSESSMENT
NDA 208246**



2) Carton Labeling N/A

3) OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: ACCEPTABLE Arthur B. Shaw Ph.D.

Secondary Review Comments and Concurrence:

**Craig M. Bertha
25-JAN-2016**

II. List of Deficiencies To Be Communicated

N/A

III. Attachments

A. Lifecycle Knowledge Management

See separate Risk Assessment III document filed on 10-FEB-2016, by ATL, for details

Risk Assessment III For Pre-Marking Application

Application #: 208246	Submission Type: 3 under 505(b)(1)	Established/Proper Name: Xeljanz® XR (tofacitinib)
Applicant: Pfizer Inc.	Letter Date: 24-APR-2015	Dosage Form: extended release tablets
Chemical Type: non-NME	Stamp Date: 24-APR-2015	Strength: 11 mg

Tofacitinib is an inhibitor of the Janus kinase (JAK) family of kinases and is said to block signaling leading to certain immune responses associated with rheumatoid arthritis (treatment indication). The tofacitinib drug product is formulated using “extrudable core system” technology. (b) (4)

(b) (4)

(b) (4)

Note that the labeling indicates that patients receiving the drug product “may notice an inert tablet shell passing in the stool or via colostomy.”

Risk Assessment III For Pre-Marking Application (N208246)

DP attribute/ CQA	Factors that can impact the CQA	O ¹	S ²	D ²	FMECA RPN #	Comment & considerations
Identification	- incorrect drugs formulated - no drug formulated	2	3	1	6	- Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substance include a specific (IR spectra relative to reference standard) and non-specific (LC retention time) identification tests - Severity of failure would depend on situation (incorrect or no drug present)² - Final drug product specification includes two non-specific tests for the drug for identity confirmation (UV spectral comparison and LC retention time comparison to standards)
Appearance	- Coating weight/color (b) (4) - Desiccant (b) (4) - Tablet printing	2	3	3	18	(b) (4) (b) (4) (b) (4) - No detail provided for how it is assured that 100% of packages (b) (4) and appropriate sampling plan will be in place); Pfizer Pharmaceuticals LLC at Vega Baja (FEI: 2623619) packaging (TTR) operations were covered during the last inspection conducted on 19-JUN-2015 (facility deemed acceptable)
Assay	- input purity of API - input purity of excipients impacting API stability as formulated	4	3	2	24	- Total impurities allowed in input API limited by respective specification (total of NMT (b) (4) %) - Excipients are of compendial quality, i.e., suitable for solid oral dosage forms - GMP adherence should prevent incorrect API amount

¹ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

² Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

Risk Assessment III For Pre-Marking Application (N208246)

	- incorrect amounts of API formulated - impurity formation due to interaction of drugs with excipients or catalyzed by excipients - degradation of drug substance due to environmental factors (b) (4) - Tablet weight					formulated - Applicant does address API and excipient compatibility in P.2.1.2, and this can be gauged indirectly based on drug product stability data (b) (4)
Physical stability (solid state of API, dosage form)	polymorphic conversion of drug substance	1	3	5	15	- A polymorph screen (see N203214) has only found the (b) (4) - Drug product manufacturing involves (b) (4) - Tests of drug product unlikely to (b) (4)
Content uniformity	(b) (4)	2	3	3	18	- Although applicant has assessed (b) (4) during development (and CU with stratified sampling), they do not propose routine (b) (4) will be monitored by CU with stratified sampling; (b) (4) - There are enough data generated during development and at commercial scale to address (b) (4) and CU; (b) (4) not needed as long as stratified CU is being used (b) (4) - Content uniformity is tested as part of drug product specification as per USP <905> (b) (4)

Risk Assessment III For Pre-Marking Application (N208246)

Microbial limits ³	- microbial load of input materials for formulation - microbial contamination during processing - microbial growth during shelf life	1	3	3	9	- Applicant claims in P.2 (see table P.2-2) that they use USP microbial limits testing for input excipients - GMP cleaning validation to address contamination potential during processing - Applicant proposes not to test the drug product for microbial properties; they claim total microbial and mold and yeast counts of NMT (b) (4) cfu and absence of <i>E. coli</i> per (b) (4) for samples of drug product tested (including stability samples); product formulation (b) (4) thus, the risk associated with the microbial contamination is low (b) (4); microbial test with bacteria, molds and yeasts were found to be within the limit for stability testing according to USP <61> and USP <62> (b) (4) bacteria and (b) (4) molds and yeasts)
Alcohol Dose Dumping	extended release properties compromised in the presence of ethanol	2	3	4	24	<i>In vitro</i> dissolution data indicate that increasing levels of ethanol lead (b) (4)
Drug Release or Dissolution	(b) (4) coating composition, amount, and integrity (b) (4) coating application process variability - absence of (b) (4) drilled hole - variability of depth of (b) (4) drilled hole - tablet hardness - polymorph conversion - changes in input excipients and APIs - API particle size	1	3	3	9	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

³ Evaluation to be done by the microbiology team.

Risk Assessment III For Pre-Marking Application (N208246)

	- change (b) (4) - DOEs to define proven acceptable ranges (PARs) for process parameters are based on “acceptable” dissolution results (biopharmaceutics review pending)						3.3.P.3.3) (b) (4) is monitored in-process (b) (4) - API particle size is assessed as per drug substance specification: (b) (4) - Excipients are also of compendial grade and in common use - Drug product specification includes an assessment (b) (4) - If DOEs to define PARs are based on dissolution results that are deemed too highly variable (biopharm review pending), the risk to product variability in terms of other CQAs, besides and including dissolution, may be higher; however, during the inspection, we evaluated the DOE study, and asked the firm to tighten some of the PARs as a result; based on the current PARs, the <u>average dissolution results</u> are within the revised specification of the dissolution
(b) (4)	(b) (4)	2	3	2	12		

Risk Assessment III For Pre-Marking Application (N208246)

	(b) (4)							(b) (4)
(b) (4)	Parameters of film coating processes (b) (4)	3	3	2	18			(b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

Risk Assessment III

Craig M. Bertha
CMC Lead for DPARP, DNDP/OPQ
10-FEB-2016

Craig M.
Bertha -S

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PANORAMA

My Work Projects Reporting Requests Timesheet

NDA 208246-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Task Summary

Task Details

Issues

Updates

Inspection Management Form

Inspection Management Form

As of 3:24 PM

Inspection Management Form

NDA 208246-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)

PFIZER PHARMACEUTICALS LLC | 2623619 | CTL CONTROL TESTING LABORATORY | Approve Facility ~

PFIZER PHARMACEUTICALS LLC | 2623619 | TTR TABLETS, EXTENDED RELEASE | Approve Facility ~

PFIZER PHARMACEUTICALS LLC | 2627266 | TTR TABLETS, EXTENDED RELEASE | Approve Facility ~

PFIZER IRELAND PHARMACEUTICALS RINGASKIDDY API PLANT | 3002307852 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility ~

PFIZER INC | 3003836868 | CTL CONTROL TESTING LABORATORY | Approve Facility ~

PFIZER IRELAND PHARMACEUTICALS RINGASKIDDY API PLANT | 3003882524 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | ~

Overall Manufacturing Inspection Recommendation

☒ Approve
☐ Withhold

Cancel

Edit Task | Task Actions

Assigned To



OPF Reviewer



Yong Hu



IM - OPF Reviewer

Edit Assignment

This was done on
Jan 25, 2016
(23 days ago)Status
Complete

Requested by



DARRTS Integration

This task is waiting on
FacilitiesLast Update
Jan 25, 2016Submitted On
Apr 25, 2015Reference Number
4478997

Risk Assessment II For Pre-Marking Application

Application #: 208246	Submission Type: 3 under 505(b)(1)	Established/Proper Name: Xeljanz® XR (tofacitinib)
Applicant: Pfizer Inc.	Letter Date: 24-APR-2015	Dosage Form: extended release tablets
Chemical Type: non-NME	Stamp Date: 24-APR-2015	Strength: 11 mg

Tofacitinib is an inhibitor of the Janus kinase (JAK) family of kinases and is said to block signaling leading to certain immune responses associated with rheumatoid arthritis (treatment indication). The tofacitinib drug product is formulated using “extrudable core system” technology. (b) (4)

(b) (4)

Note that the labeling indicates that patients receiving the drug product “may notice an inert tablet shell passing in the stool or via colostomy.”

Risk Assessment II For Pre-Marking Application (N208246)

DP attribute/ CQA	Factors that can impact the CQA	O ¹	S ²	D ²	FMECA RPN #	Comment & considerations
Identification	- incorrect drugs formulated - no drug formulated	2	3	1	6	- Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specification for drug substance include a specific (b) (4) relative to reference standard) and non-specific (LC retention time) identification tests - Severity of failure would depend on situation (incorrect or no drug present)² - Final drug product specification includes two non-specific tests for the drug for identity confirmation (b) (4) comparison and LC retention time comparison to standards)
Appearance	- Coating weight/color (b) (4) - Desiccant (b) (4) - Tablet printing	2	3	5	30	- In-process testing includes (b) (4) (b) (4) (b) (4) (b) (4) - No detail provided for how it is assured that 100% of packages (b) (4) and appropriate sampling plan will be in place)
Assay	- input purity of API - input purity of excipients impacting API stability as formulated - incorrect amounts of API formulated - impurity formation due to interaction of drugs	4	3	2	24	- Total impurities allowed in input API limited by respective specification (total of NMT (b) (4) %) - Excipients are of compendial quality, i.e., suitable for solid oral dosage forms - GMP adherence should prevent incorrect API amount formulated - Applicant does address API and excipient compatibility in P.2.1.2, and this can be gauged indirectly based on drug product stability data

¹ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

² Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

Risk Assessment II For Pre-Marking Application (N208246)

	- with excipients or catalyzed by excipients - degradation of drug substance due to environmental factors (b) (4) - Tablet weight				30	(b) (4) (b) (4) (b) (4)
Physical stability (solid state of API, dosage form)	polymorphic conversion of drug substance	2	3	5	30	- A polymorph screen (see N203214) has only found the (b) (4) - Drug product manufacturing involves (b) (4) - Tests of drug product unlikely to (b) (4)
Content uniformity	(b) (4)	3	3	3	27	- Although applicant has assessed (b) (4) during development (and CU with stratified sampling), they do not propose routine (b) (4) (will likely be evaluated relative to 21 CFR 211.110 as part of GMP inspection) - Content uniformity is tested as part of drug product specification as per USP <905> (b) (4)
Microbial limits ³	- microbial load of input materials for formulation - microbial contamination during processing - microbial growth during shelf life	2	3	5	30	- Applicant claims in P.2 (see table P.2-2) that they use USP microbial limits testing for input excipients - GMP cleaning validation to address contamination potential during processing - Applicant proposes not to test the drug product for microbial properties; they claim total microbial and mold and yeast counts of NMT (b) (4) cfu and absence of <i>E. coli</i> per (b) (4) for samples of drug product tested (including stability samples)
Alcohol Dose	extended release properties compromised	2	3	4	24	<i>In vitro</i> dissolution data indicate that increasing levels of ethanol lead to (b) (4)

³ Evaluation to be done by the microbiology team.

Risk Assessment II For Pre-Marking Application (N208246)

Dumping		in the presence of ethanol					
Drug Release or Dissolution	• (b) (4) • composition, amount, and integrity • (b) (4) • application process variability • absence of (b) (4) drilled hole • variability of depth of laser drilled hole • tablet hardness • polymorph conversion • changes in input excipients and APIs • API particle size change • (b) (4) • DOEs to define proven acceptable ranges (PARs) for process parameters are based on “acceptable” dissolution results (biopharmaceutics review pending)	4	3	3	36	• (b) (4) • (b) (4) • (b) (4) • (b) (4) • (b) (4) • (b) (4) • (b) (4) • (b) (4) is monitored in-process • (b) (4) • API particle size is assessed as per drug substance specification: (b) (4) • Excipients are also of compendial grade and in common use • Drug product specification includes an assessment (b) (4) • If DOEs to define PARs are based on dissolution results that are deemed too highly variable (biopharm review pending), the risk to product variability in terms of other COAs. besides and including dissolution. may be higher (b) (4)	
(b) (4)	• (b) (4) • (b) (4) • (b) (4)	3	3	5	45	• (b) (4) • (b) (4) • (b) (4)	

Risk Assessment II For Pre-Marking Application (N208246)

		(b) (4)						•	(b) (4)
								•	
(b) (4)	• Parameters of film coating processes (b) (4)	3	3	2	18		•		
							•		

OFFICE OF PHARMACEUTICAL QUALITY

Risk Assessment II

Craig M. Bertha
CMC Lead

Craig M.
Bertha -S

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ou=HHS, ou=FDA, ou=People,
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Date: 2015.09.18 06:12:53 -04'00'