DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203214/S-018

SUPPLEMENT APPROVAL

PF PRISM C.V.
C/o Pfizer, Inc.
Attention: Louis M. Ferrara
Director, Worldwide Regulatory Strategy
445 Eastern Point Road
Groton, CT 06340

Dear Mr. Ferrara:

Please refer to your supplemental New Drug Application (sNDA) dated May 4, 2017, received May 4, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for XELJANZ (tofacitinib), 5 mg and 10 mg tablets.

We acknowledge receipt of your major amendment dated September 28, 2017, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication

Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 10, 2018, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric studies requirement for ages less than 2 years because necessary studies are impossible or highly impracticable. This is because there is a low incidence of the disease in this age group. In addition, difficulties exist in differentiating the subtypes of inflammatory bowel disease in infants and very young children.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3400-1 A one-year, multi-center, randomized, controlled trial to evaluate the safety, efficacy and pharmacokinetics of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	04/2022
Final Report Submission:	09/2022

3400-2 A multi-center open-label extension study to evaluate the long-term safety of XELJANZ (tofacitinib) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in PMR 3400-1.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	03/2024
Final Report Submission:	08/2024

Submit the protocol(s) to your IND 111294, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious

risk of malignancies associated with the long-term use of XELJANZ (tofacitinib) in the treatment of adults with moderate to severe ulcerative colitis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, you are required to conduct the following:

3400-3 A long-term, observational study to assess the long-term safety of tofacitinib 5mg BID or 10mg BID versus other therapies used in the treatment of adults with moderately to severely active ulcerative colitis. The study's primary outcome is malignancy. Secondary outcomes of interest include, but are not limited to, opportunistic infections, thromboembolic events, and hepatic injury. Specify concise case definitions, and provide outcome validation for both primary and secondary outcomes. Describe and justify choice of appropriate comparator population(s) and estimated background rates relative to tofacitinib-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the tofacitinib-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 18 months of tofacitinib exposure at the end of the study. Follow for period of at least 7 years.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2018
Final Protocol Submission:	01/2019
Study Completion:	01/2026
Interim Report:	01/2023
Final Report Submission:	06/2026

Submit the protocol(s) to your IND 111294, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3400-4 A double-blind, randomized, controlled clinical trial to assess the relative efficacy of XELJANZ (tofacitinib) 5mg BID versus 10mg BID for maintaining remission in patients with moderate to severe ulcerative colitis who are in stable remission for at least 6 months on XELJANZ (tofacitinib) 10mg BID therapy.

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2018
Final Protocol Submission:	12/2018
Study/Trial Completion:	01/2024
Final Report Submission:	07/2024

3400-5 A controlled clinical trial to assess both the clinical and immunological responses to Shingrix vaccination in adult patients with moderately to severely active ulcerative colitis treated with XELJANZ (tofacitinib).

The timetable you submitted on May 29, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	03/2019
Study/Trial Completion:	05/2022
Final Report Submission:	11/2022

Submit clinical protocols to your IND 111294 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, M.M.Sc.
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

JESSICA J LEE
05/30/2018