DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202570

ACCELERATED APPROVAL

Pfizer Inc.
Attention: Ron C. Domingo, M.S., RAC
Manager
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Mr. Domingo:

Please refer to your New Drug Application (NDA) dated March 30, 2011, received March 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XALKORI® (crizotinib) Capsules, 200 mg and 250 mg.

We acknowledge receipt of your amendments dated January 4, 2011; February 22, 2011; February 24, 2011; March 31, 2011; April 13, 2011; April 15, 2011; April 26, 2011; May 3, 2011; May 19, 2011; May 24, 2011; May 26, 2011; June 6, 2011; June 8, 2011; June 9, 2011; June 13, 2011; June 14, 2011; June 15, 2011; June 17, 2011; June 23, 2011; June 24, 2011; June 30, 2011; July 1, 2011 (2); July 6, 2011; July 7, 2011; July 12, 2011; July 13, 2011 (2); July 15, 2011; July 21, 2011; July 22, 2011; July 26, 2011; July 27, 2011; August 1, 2011 (2); August 2, 2011(2); August 3, 2011; August 5, 2011; August 8, 2011; August 10, 2011; August 11, 201l; August 12, 2011; August 15, 2011; August 17, 2011; August 18, 2011; August 23, 2011 (2); August 24, 2011, and August 26, 2011.

This new drug application provides for the use of XALKORI (crizotinib) Capsules, 200 mg and 250 mg, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

Based on the stability data provided in your application, the drug product is granted a fifteen (15) month expiry as packaged in the proposed commercial configuration (60 count/HDPE bottle) when stored at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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, text for the patient package insert). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABELS

We acknowledge that your March 30, 2011, submission contains final printed container labels that will be used during the initial launch.

We note your agreement on August 3, 2011, and August 23, 2011, to revise your container labels at the next printing September 2011, to unbold and relocate the "Rx only" wording to the bottom of the label and to change the wording on the left side panel to read "Store at room temperature 20º to 25º C (68º to 77º F); excursions permitted between 15º to 30º C (59º to 86º F) [see USP Controlled Room Temperature]". We acknowledge that your August 24, 2011, submission contains final printed container labels with these changes to be used at next printing.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for XALKORI (crizotinib) Capsules, 200 mg and 250 mg, was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. We remind you of your postmarketing requirement specified in your submission dated August 1, 2011. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by XALKORI (crizotinib) Capsules, 200 mg and 250 mg, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530(b), withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical trials to verify the clinical benefit of XALKORI (crizotinib) Capsules, 200 mg and 250 mg. These postmarketing trials are subject to the reporting requirements of 21 CFR 314.81. These requirements, along with required completion dates, are listed below.

1789-1

Clinical trial report and datasets from A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of PF-02341066 vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-2

Clinical trial report and datasets from A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

Final Protocol Submission:	06/2010 (submitted)
Trial Completion:	12/2015
Final Report Submission:	06/2016

Submit clinical protocols to your IND 73544, with a cross reference letter to this NDA. Submit all final reports to this NDA as supplemental applications. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 identify an unexpected serious risk of drug interactions caused by the induction of human CYP2B and CYP2C enzymes by XALKORI (crizotinib) Capsules, 200 mg and 250 mg.

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, FDA has determined that you are required to conduct the following:

1789-3

Submit the final report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.

The timetable you submitted on August 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2011
Study Completion:	12/2011
Final Report Submission:	12/2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of visual disorders with XALKORI (crizotinib) Capsules, 200 mg and 250 mg, and to assess signals of a serious risk of QT prolongation, drug-drug interactions with CYP3A inhibitors and inducers and gastric pH elevating drugs, and increased concentrations of XALKORI (crizotinib) Capsules, 200 mg and 250 mg in patients with hepatic impairment or severe renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1789-4

Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied. The following examinations should be performed in these patients at baseline, 2 and 6 weeks after drug administration and 2-8 weeks after discontinuation of the therapy (single visit post therapy).

1. Best corrected distance visual acuity
2. Refractive error associated with best corrected distance visual acuity
3. Pupil size under standardized lighting conditions
4. Slit lamp biomicroscopy of the anterior segment
5. Intraocular pressure
6. Ocular coherence tomography of the macula
7. Dilated fundus photography of the retina

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2011
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-5

Complete the ECG sub-study in trial A8081007 and submit the final report, along with a thorough review of cardiac safety data to address any potential impact of crizotinib on QTc interval prolongation in patients.

The timetable you submitted on August 3, 201l, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-6

Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inhibitor (*e.g.,* ketoconazole).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-7

Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inducer (*e.g.*, rifampin).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-8

Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	09/2011
Trial Completion:	07/2013
Final Report Submission:	01/2014

1789-9

Conduct a trial in humans to determine the appropriate crizotinib dose in patients with severe renal impairment.

The timetable you submitted on August 12, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	09/2011
Trial Completion:	04/2012
Final Report Submission:	10/2012

1789-10

Conduct a trial in humans to determine how to dose crizotinib with regard to gastric pH elevating agents (*i.e.*, a proton-pump inhibitor, an H2-receptor antagonist, and an antacid).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	01/2012
Trial Completion:	03/2013
Final Report Submission:	09/2013

Submit the protocols to your IND 073544, with a cross-reference letter to this NDA. Submit all final reports 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)"**.

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:

1789-11

To assess the adequacy of the current cut-off, conduct a clinical trial to explore response to crizotinib in ALK-negative patients based on current assay cut-off. This should be compared to historic controls and to the response in ALK-positive patients. Additional biomarkers should be assessed in ALK-negative patients.

The timetable you submitted on August 24, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2011
Trial Completion:	05/2013
Final Report Submission:	11/2013

1789-12

To conduct exposure-response analysis for progression-free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081007 and to submit the analysis plan for review.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2009 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-13

To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081014 and to submit the analysis plan for review.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2010 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2015
Final Report Submission:	06/2016

Submit clinical protocols to your IND 073544 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
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/

RICHARD PAZDUR
08/26/2011