DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203388

NDA APPROVAL

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Rohrer:

Please refer to your New Drug Application (NDA) dated September 8, 2011, received September 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ERIVEDGE (vismodegib) capsule, 150 mg.

We acknowledge receipt of your amendments dated through January 30, 2012.

This new drug application provides for the use of ERIVEDGE (vismodegib) capsule for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

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

Based on the provided stability data, an expiration dating period of 24 months is granted for the drug product when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F 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 for the package insert and Medication Guide. 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and container labels submitted on December 22, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203388**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with 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 ERIVEDGE (vismodegib) capsule was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since basal cell carcinoma is rare in the 0-18 year old age group.

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 carcinogenicity or assess a signal of a serious risk of teratogenicity.

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:

PMR 1862-1: To conduct a rodent carcinogenicity study in the mouse. Prior to initiating the study, you will submit and receive agreement on the carcinogenicity protocol under a Special Protocol Assessment (SPA).

The timetable you submitted on January 26, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	October 2012
Final Report Submission:	October 2017

PMR 1862-2: To conduct a long-term rodent carcinogenicity study in the rat. Prior to initiating the study, you will submit and receive agreement on the carcinogenicity protocol under a Special Protocol Assessment.

The timetable you submitted on January 26, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	October 2012
Final Report Submission:	October 2017

PMR 1862-3: To conduct a Pregnancy Pharmacovigilance Study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to vismodegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to vismodegib as treatment) and indirect exposures (women exposed to vismodegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. The registry and study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.
- Description of registry procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of pregnancy registry, and the monitoring of pregnancy and infant outcomes.

Each interim and final report should constitute a stand-alone report of cumulative registry outcomes data.

The timetable you submitted on January 26, 2012, states that you will conduct this study according to the following schedule:

Final Pregnancy Pharmacovigilance Study Protocol:	May 2012
Annual Interim Report Submission for nine years:	May 2013
	May 2014
	May 2015
	May 2016
	May 2017
	May 2018
	May 2019
	May 2020
	May 2021
Final Report Submission:	May 2022

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased toxicity in patients with impaired renal or hepatic function and an unexpected serious risk of toxicity from potential drug-drug interactions.

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

PMR 1862-4: To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function–Study Design, Data Analysis and Impact on Dosing and Labeling". The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the trial should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on January 26, 2012 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	February 2012
Trial Completion:	September 2014
Final Report Submission:	March 2015

PMR 1862-5: To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function–Study Design, Data Analysis and Impact on Dosing and Labeling." A "reduced" renal impairment trial could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the trial should be sufficient to detect

PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on January 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	February 2012
Trial Completion:	September 2014
Final Report Submission:	March 2015

PMR 1862-6: To submit a final report for the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone).

The timetable you submitted on January 26, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission:	March 2012

PMR 1862-7: To conduct a drug-drug interaction clinical trial in healthy volunteers to evaluate if gastric pH elevating agents alter the bioavailability and impact the steady-state exposure of vismodegib. The trial may be conducted in a gated manner, first evaluating the effect of proton pump inhibitors (PPIs) on the steady state exposure of vismodegib. In the event that concomitant administration of PPIs has a large impact on vismodegib steady state exposure, H2 antagonists and antacids will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect PK differences. The trial results should allow for a determination on how to dose vismodegib with regard to gastric pH elevating agents.

The timetable you submitted on January 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2013
Trial Completion:	August 2014
Final Report Submission:	February 2015

Submit the protocols to your IND 74573, 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.

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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.

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 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. We note your request to hold a post-action feedback meeting. We will arrange a date and time to hold the meeting.

If you have any questions, call Dr. Mona Patel, Regulatory Project Manager, at (301) 796-4236.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
- Package Insert
- Medication Guide
- 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
01/30/2012