

**CENTER FOR DRUG EVALUATION AND
RESEARCH AND CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH**

APPLICATION NUMBER:
125147/0

APPROVAL LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125147/0

SEP 27 2006

Amgen, Incorporated
Attention: Alessandra Cesano, M.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cesano:

We have approved your biologics license application for Panitumumab effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Panitumumab under your existing Department of Health and Human Services U.S. License No.1080. Panitumumab is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Under this license, you are approved to manufacture Panitumumab drug substance at your facility in Fremont, CA. The final formulated drug product will be manufactured at the [REDACTED]. The final formulated drug product will be labeled and packaged at [REDACTED]. You may label your product with the proprietary name Vectibix™ and will market it as a 5mL single-use vial containing 100 mg Panitumumab (20mg/mL), a 10mL single-use vial containing 200 mg Panitumumab (20mg/mL), and as a 20mL single-use vial containing 400 mg Panitumumab (20mg/mL).

The dating period for Panitumumab shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 24 months when stored at 2-8 °C. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Panitumumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Panitumumab, or in the manufacturing facilities.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement under the Pediatric Research Equity Act (PREA).

As requested in your letter of May 12, 2006, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Panitumumab, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw or modify approval.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

Granting of this approval is contingent upon completion of clinical studies to verify the clinical benefit of Panitumumab, as outlined in your letter of September 22, 2006:

1. To submit a final study report for study 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer" which is intended to verify the clinical benefit of Panitumumab through demonstration of an effect on overall survival (OS). This protocol was accepted for Special Protocol Assessment on May 3, 2006. Patient accrual began on June 30, 2006, and will be completed by September 30, 2009. The final study report will be submitted by March 30, 2010.

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of September 22, 2006.

For administrative purposes, all submissions related to this postmarketing study should be clearly designated "Subpart E Postmarketing Study Commitments."

In addition, we acknowledge your written commitments as described in your letter of September 22, 2006, as outlined below:

2. To conduct a Phase 1 study, Protocol 20050252 entitled, “A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Panitumumab in Children with Refractory Solid Tumors” in children and adolescents (up to 18 yr of age) to provide the initial safety assessment and establish the pharmacokinetics in pediatric patients with solid tumors in which, based on clinical study and published literature information, an EGFr inhibitor drug has been shown to have clinical activity.

A draft protocol will be submitted by November 20, 2006, a final protocol will be submitted by July 30, 2007, patient accrual will begin by October 31, 2007, the study will be completed by April 10, 2011, and the final study report will be submitted by October 31, 2011.

3. Based on the results of the Phase 1 protocol 20050252 (i.e., provided that a safe and tolerable dose of Panitumumab can be determined for children), Amgen will conduct a Phase 2 study to further assess the safety and to estimate the anti-tumor activity of Panitumumab in pediatric patients with solid tumors in which, based on clinical study and published literature information, an EGFr inhibitor drug has been shown to have clinical activity.

A draft protocol will be submitted by December 15, 2010. A final protocol will be submitted by August 15, 2011, patient accrual will begin by December 30, 2011, the study will be completed by December 30, 2013, and the final study report will be submitted by May 30, 2014.

4. To submit a summary of the final results of overall survival (OS), with 12-month minimal follow up from Study 20020408, entitled, “An Open Label Randomized, Phase 3 Clinical Trial of ABX-EGF Plus Best Supportive Care Versus Best Supportive Care in Subjects With Metastatic Colorectal Cancer.” This will include only the survival data. It will be followed by submission of the final clinical study report, including 24-month follow up of overall survival. The final protocol was submitted on July 16, 2003, patient accrual began January 16, 2004. The study will be completed by March 15, 2007, an interim study report including 12 month OS data will be submitted by October 30, 2006, and the final study report will be submitted by September 30, 2007.

5. To submit interim and final clinical study reports based on data obtained in study 20050181, entitled, “A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer”, that addresses clinical utility of EGFR testing with the Dako PharmDx EGFR kit as a means for selecting patients who will benefit when treated with Panitumumab. The report will include both summary analyses of safety and efficacy as a function of EGFR test results and primary datasets. This protocol was reviewed under Special Protocol Assessment and accepted by FDA on May 3, 2006. Patient accrual began on June 30, 2006, the study will be completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.
6. To submit interim and final clinical study reports based on data obtained in study 20050181, entitled, “A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer”, characterizing the toxicity profile of the commercially marketed product. The report will include comparative analyses of safety between study arms, case report forms for all patients with deaths during treatment or who discontinued treatment or underwent dose modification of Panitumumab for adverse events, narrative summaries for all serious adverse events, and summary data characterizing Panitumumab and chemotherapy drug exposure (e.g., dose intensity over fixed time periods). In addition, primary data will be provided in SAS-compatible electronic datasets. This protocol was reviewed under Special Protocol Assessment and accepted by FDA on May 3, 2006. Patient accrual began on June 30, 2006, the study will be completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.
7. To submit interim and final clinical study reports based on data obtained in study 20050181, entitled, “A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer” characterizing the immunogenicity profile of the commercial product, and impact of anti-Panitumumab binding and neutralizing antibodies on the pharmacokinetic, safety and efficacy profile of Panitumumab. The report will include both summary analyses and the primary datasets used to generate the summary analyses, in electronic, SAS-compatible format. This protocol was accepted for Special Protocol Assessment on May 3, 2006. Patient accrual began on June 30, 2006, the study will be completed (PFS data cut off) by February 28, 2008. An interim study report will be provided by August 30, 2008, and a final study report will be submitted by March 30, 2010.

8. To submit a final study report for study 20050184, entitled “A Phase 2, Open-label, Randomized Clinical Trial of Skin Toxicity Treatment of Subjects Receiving Second-line FOLFIRI or Irinotecan Only Chemotherapy Concomitantly with Panitumumab” containing an evaluation of the clinical management of Panitumumab-induced skin toxicities. The report will include both summary analyses of safety as a function of medical management and primary datasets from this study and from any reference studies used for comparative safety analyses, which will include information on medical interventions and toxicity onset, severity and clinical course. The final protocol was submitted on March 28, 2006. Patient accrual began on April 19, 2006, and the study will be completed by May 15, 2008. A final study report will be submitted by November 30, 2008.
9. To conduct a Phase 1 drug interaction study 20062010, entitled “Open Label, 2-Cohort, Randomized Study to Assess the Potential Pharmacokinetic Drug-Drug Interaction between Irinotecan and Panitumumab in Subjects with Colorectal Cancer” which will provide a formal assessment of pharmacokinetic (PK) drug-drug interactions. The final study report will provide summary analyses of pharmacokinetic and safety information and primary data used to generate the analyses in an electronic, SAS-compatible dataset. The final protocol will be submitted by August 31, 2007. Patient accrual will begin by December 31, 2007, and the study will be completed (last PK sample for last enrolled patient) by April 1, 2009. The final study report will be submitted by August 30, 2009.
10. To submit a final study report for study 20040192 entitled, “A Phase 1 Clinical Study of ABX-EGF (Panitumumab) Evaluation of the Safety and PK of ABX-EGF in Japanese Subjects with Advanced Solid Tumors” that characterizes the pharmacokinetic profile of Panitumumab in the Japanese population. The final study report should provide summary analyses and primary data, including pharmacokinetic data, in both the Japanese and non-Asian population that will permit an assessment of differences in pharmacokinetics, if any, based on race/ethnicity. The study will be completed (database lock) by June 30, 2006, and the final study report will be submitted by April 1, 2007.

11. To submit an assessment and the following information regarding the role of EGFr in post-natal lung, gastrointestinal, neurologic, bone, or pancreatic development in humans.
 - a. Copies of all published literature reports of nonclinical or clinical data addressing the role of EGFr in post-natal human respiratory and gastrointestinal tract, neurologic, skeletal, and endocrine development.
 - b. Identification (by Study Number) of any previously submitted final study reports, and submission of any additional data (including primary data) from non-clinical studies of Panitumumab conducted by, or under a contractual arrangement for, Amgen in young (pre-pubertal) non-human primates. These data, including all findings in respiratory and gastrointestinal tract, and neurologic, bone, and endocrine organs from any Panitumumab-treated juvenile animals from the aforementioned studies, will be summarized and discussed in context of toxicities observed in adult human respiratory and gastrointestinal tract, neurologic, skeletal, and endocrine organ systems.

The assessment, including all literature references, will be submitted by November 30, 2006.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:

12. To submit proposed revisions to release specifications and shelf-life specifications for Panitumumab drug substance after █ commercial manufacturing runs. A summary of the test results will be submitted annually by April 30, 2007 and April 30, 2008. The proposed revisions to the quality control system, data from the █ commercial manufacturing runs, and the analysis plan used to support the proposed specifications will be submitted as a supplement to the BLA no later than June 30, 2008.
13. To submit proposed revisions to release specifications and shelf-life specifications for Panitumumab drug product after █ commercial manufacturing runs. A summary of the test results will be submitted annually by April 30, 2007 and April 30, 2008. The proposed revisions to the quality control system, data from the █ commercial manufacturing runs, and the analysis plan used to create the proposed specifications will be submitted as a supplement to the BLA no later than December 31, 2007.
14. To include container-closure integrity (CCI) testing as a component of the post approval drug product stability program using each vial configuration (5 mL, 10 mL, 20 mL) as they are added to the stability program, with testing at the █ month time-points to demonstrate CCI throughout shelf life. A revised stability protocol to include CCI testing will be submitted in a supplement by September 30, 2007.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125147. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125147. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fnl.htm>) for further information.

In addition, we acknowledge your agreement to do the following:

15. To oversee the implementation of design and facility controls at the [REDACTED] facility in [REDACTED] as stated in your September 6, 2006, submission. You agree to implement these changes prior to the production of the first batch by December 31, 2006. Information regarding the implementation of these changes to the facility design and contamination control procedures will be provided in the first annual report submitted to the BL STN 125147.

These changes may be submitted annually in your annual report per 21 CFR 601.12 (d). Such reports should provide relevant data pertaining to [REDACTED] manufacturing, including data on [REDACTED]

(b)(4)

16. To perform and submit a stability assessment of the [REDACTED] at the [REDACTED] time point [REDACTED], and the [REDACTED] time point [REDACTED] and every [REDACTED] thereafter. The results of this assessment will be submitted to the appropriate annual report. The first assessment will be submitted no later than April 30, 2007.
17. To perform stability testing of one drug substance lot annually for each year in which Panitumumab drug substance is manufactured, As part of the post approval commitment, the ongoing stability program will continue until testing of all remaining time-points from the lots used to support the approved shelf life have been reached. For your convenience, you may include this information in your annual reports, the first to be submitted by April 30, 2007. Additionally, lots that are manufactured following significant changes to the approved manufacturing process or facility, the first lot that is [REDACTED] [REDACTED] step and lots that are reprocessed outside of the approved manufacturing process will be placed on stability.
18. To perform stability testing on at least one marketed drug product lot; annually. Lots will be randomly selected and placed on stability. Vial presentations selected will vary from year to year to ensure a balanced program. For your convenience, you may include this information in your annual reports, the first to be submitted by April 30, 2007. In the event that no drug product from a particular vial presentation was manufactured during a given year, a stability study is not required. Additionally, lots that are manufactured following any significant changes to the approved manufacturing process or facility, and lots that have been reprocessed outside of the approved manufacturing process will be placed on stability.

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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 www.fda.gov/medwatch/report/mmp.htm. You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and the submitted labeling (immediate container submitted on September 20, 2006, and carton labels submitted on September 22, 2006). Marketing product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit within 30 days content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text dated September 26, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Sincerely,

A handwritten signature in black ink that reads "Richard Pazdur MD". The signature is written in a cursive style with a large, prominent "R" and "P".

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

Enclosure: Package Insert Labeling
Carton and Vial Labeling