CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125084/0

FEB 12 2004

ImClone Systems, Incorporated
Attention: Lily Lee, Ph.D.
Vice President, Regulatory Affairs and Biostatistics
Branchburg Corporate Center
33 Chubb Way
Branchburg, NJ 08876

Dear Dr. Lee:

We are issuing Department of Health and Human Services U.S. License No. 1695 to ImClone Systems, Incorporated, Branchburg, NJ, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Cetuximab. Cetuximab, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Cetuximab, administered as a single agent, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy. The effectiveness of Cetuximab is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Cetuximab.

Under this license, you are approved to manufacture Cetuximab at [redacted] (b)(4) The drug substance will be formulated, filled, labeled, and packaged at (b)(4) You may label your product with the proprietary name ERBITUX and will market it as a 50 mL vial containing 100 mg (2 mg/mL).

The dating period for Cetuximab shall be 36 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 12 months when stored at 2-8°C. The stability protocols in your license application are considered approved for the purposes of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You currently are not required to submit samples of future lots of Cetuximab 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 Cetuximab, or in the manufacturing facilities.

As requested in your letter of January 27, 2004, 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 the 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 Cetuximab, or are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical studies to verify the clinical benefit of Cetuximab therapy, as outlined in your letter of February 6, 2004. These postmarketing studies are subject to the reporting requirements of 21 CRF 601.70:

1. To complete Protocol CA225006, "A Phase III, Randomized, Open-Label, Multicenter Study of Irinotecan and Cetuximab versus Irinotecan as Second-Line Treatment in Patients with Metastatic, EGFR-Positive Colorectal Carcinoma." This protocol was accepted for Special Protocol Assessment on April 25, 2003. Patient accrual will be completed by June 30, 2005, the study will be completed by December 31, 2006, and final study report submitted by June 30, 2007.

2. To complete Protocol CA225014, "A Phase III, Randomized, Multicenter Study of Cetuximab, Oxaliplatin, 5-FU, and Leucovorin versus Oxaliplatin, 5-FU, and Leucovorin in Patients with Previously Treated Metastatic, EGFR-Positive Colorectal Carcinoma." This protocol was accepted for Special Protocol Assessment on February 28, 2003. Patient accrual will be completed by December 31, 2006, the study will be completed by September 30, 2008, and the final study report submitted by March 31, 2009.

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

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 deferring submission of your pediatric studies for children and adolescents until December 31, 2007. Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 601.70. This commitment is listed below:

3. To conduct a dose finding study in children and adolescents who have EGFR-expressing, treatment refractory, pediatric solid tumors. From the screening process of this study you will begin to assess the frequency of EGFR expression in the common pediatric solid tumors. Based on the results of the Phase 1 study, you will plan and conduct Phase 2 studies in individual tumor types to determine the anti-tumor activity of Cetuximab in selected pediatric solid tumors. The Phase 1 pediatric protocol will be submitted by December 31, 2004, patient accrual will be completed by December 31, 2006, the study will be completed by June 30, 2007, and the final study report submitted by December 31, 2007.

For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitments".

In addition, we acknowledge your other written commitments described in your letter of February 6, 2004, as outlined below:

Additional Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

4. To conduct a non-clinical reproductive toxicology study of Cetuximab in monkeys. The final protocol for the Segment II monkey study will be submitted by March 31, 2005, the study will be completed by March 31. 2006, and the final study report submitted by June 30, 2006.

5. To submit data validating the accuracy, precision, sensitivity, specificity, and robustness of the immunogenicity assay to be used in establishing the incidence of patient immune response to Cetuximab. The validation report will be submitted by June 30, 2004.

6. To conduct a study to characterize the immune response to Cetuximab using a validated immunogenicity assay. We acknowledge your plan to amend an ongoing study, Protocol CA225045, "An Exploratory Pharmacogenomic Study of Cetuximab Monotherapy in Patients with Metastatic EGFR-positive Colorectal Carcinoma" to provide the necessary data on the characterization of the immune response to Cetuximab using the validated assay discussed in commitment 5 above. A protocol amendment will be submitted by March 31, 2004, patient accrual will be completed by December 31, 2004, the study will be completed by June 30, 2005, and the final study report submitted by September 30, 2005

7. To further evaluate and confirm the value of EGFR expression in tumors as a selection criteria for Cetuximab therapy in patients with metastatic colorectal cancer by conducting and submitting the results of a Phase 2 study enrolling 50-60 patients with refractory, EGFR-negative, metastatic colorectal cancer designed to estimate the overall response rate and duration obtained with single agent Cetuximab in this population. The final protocol for this study will be submitted by March 31, 2004, patient accrual will be completed by June 30, 2005, the study will be completed by December 31, 2005, and the final study report submitted by June 30, 2006.

8. To further evaluate and confirm the value of EGFR expression in tumors as a selection criteria for Cetuximab therapy in patients with metastatic colorectal cancer by submitting the data and analyzing the results obtained in a subset of patients with EGFR-negative, metastatic colorectal cancer enrolled in the protocol entitled CALGB 80203, "A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with and without Cetuximab (C225) for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum." Patient accrual will be completed by December 31, 2008, the study will be completed by December 31, 2010, and the final study report submitted by December 31, 2011.

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

9. To set (b)(4) limits for Cetuximab (b)(4) composition prior to qualification of the next Cetuximab reference standard. The study will be completed by January 31, 2005, and the final study report submitted by March 31, 2005.

10. To qualify the biochemical assays that will be used in support of the qualification of the Cetuximab reference standard. The study will be completed by January 31, 2005, and the final study report submitted by March 31, 2005.

11. To conduct additional stability studies supporting the ability of the in-line filter to remove visible particulates in Cetuximab drug product, deliver appropriate amount of drug to the patient, and not clog the filter. These studies will be conducted using representative lots of Cetuximab drug product at or beyond the 36-month expiration point as well as stressed lots for worst case analysis. The studies will be completed on August 30, 2004, and the final study report submitted on September 30, 2004.

12. To develop a quantitative assay to measure visible particulates in drug product. The validation report will be submitted on May 31, 2005.

13. To initiate a kinetic stability study on visible particulate formation. The study will be completed on April 30, 2008, and the final study report submitted on August 30, 2008.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125084. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final study reports to your BLA, STN BL 125084. 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), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

As required by 21 CFR 601.45, please 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 Division of Drug Marketing, Advertising and Communications, HFD-42, Food and Drug Administration, 5600 Fishers Lane, Rockville MD 20852. 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.

Results of ongoing stability studies should be submitted throughout the dating period as they become available. We acknowledge your intent to perform real-time, long-term stability studies on the first drug substance lot [redacted] step and on all drug substance lots [redacted] step to remove [redacted] as outlined in your stability protocol, and to submit reports on these studies to the license on a yearly basis.

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 should submit distribution reports to CBER Document Control Center, Attn: Office of Therapeutics Research and Review, Suite 200N (HFM-99), 1401 Rockville Pike, Rockville, MD 20852-1448

You must submit reports of biological product deviations under 21 CFR 600.14. You promptly should 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 regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Sincerely,

(b)(6)

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Labeling