DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125084/225

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

ImClone LLC a wholly owned subsidiary of Eli Lilly and Company
Attention: Mark Leusch, Ph.D.
Director, U. S. Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Leusch:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 7, 2011, received September 7, 2011, and submitted under section 351 of the Public Health Service Act for Erbitux (cetuximab).

We acknowledge receipt of your amendments dated September 12, October 27 and 31, November 1, 14, and 30, December 6 and 16, 2011, and January 6, February 3 and 17, March 13, June 13, 14, 22, 25 and 27, and July 2 and 6, 2012.

This "Prior Approval" efficacy supplement to your biologics license application provides for modifications to the Indications and Usage section of labeling to state that Erbitux is indicated for the treatment of patients with *K-ras* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer as determined by FDA-approved tests and to include a new limitation of use stating that Erbitux is not indicated for treatment of *K-Ras* mutation-positive colorectal cancer. In addition, this supplement provides for a new indication for Erbitux for use in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment of *K-Ras* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer.

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and include the labeling changes

proposed in any pending "Changes Being Effected" (CBE) supplements. 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.

Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

SUBPART E FULFILLED

We approved this BLA on February 12, 2004, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement, together with the October 2, 2007, approval of the supplement STN BL 125084/103, fulfills your commitment made under 21 CFR 601.41 and as stated in PMC #1 of the February 12, 2004, approval letter to verify the clinical benefit of cetuximab. We also note that, as stated in our letter of January 10, 2005, you were released from your commitment made under 21 CFR 601.41 and as stated PMC #2 of the February 12, 2004, approval letter.

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 because there are too few children with metastatic colorectal cancer to study.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1 To perform a for-cause audit of [redacted] (b) (4) and submit a detailed summary report of all aspects reviewed in the audit, an overview of specific findings, and the corrective and preventive actions that will be taken.

The timetable you submitted on June 27, 2012, states that you will conduct this audit according to the following schedule:

Audit Completion Date:	07/12
Final Report Submission:	08/12

Submit clinical protocols to your IND 5804 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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 601.12(f)(4), you must submit final promotional materials, and the package insert(s), 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.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter,

submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

PATRICIA KEEGAN
07/06/2012