DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125084/153

SUPPLEMENT BLA APPROVAL
November 7, 2011

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

Dear Dr. Leusch:

Please refer to your Supplemental Biologics License Application (sBLA), dated August 29, 2008, and received August 29, 2008, submitted under section 351 of the Public Health Service Act for Erbitux (cetuximab).

We acknowledge receipt of all subsequent amendments dated through October 24, 2011.

The September 8, 2011, resubmission constituted a complete response to our September 2, 2011, action letter.

This "Prior Approval" efficacy supplement to your biologics license application proposes a new indication for Erbitux (cetuximab) for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU.

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.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125084/153**."

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.

The SPL will be accessible via publicly available labeling repositories.

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 Federal Food, Drug, and Cosmetic Act (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.

Since Erbitux (cetuximab) was approved on February 12, 2004, we have become aware of new safety information on infusion reactions, cardiopulmonary arrest, pulmonary toxicity, and dermatologic toxicity related to differences in exposure between Erbitux (cetuximab) and the EU-approved cetuximab administered in clinical studies supporting the requested indication when administered in the same dose and schedule. In addition, the requested indication utilizes new Erbitux (cetuximab)-chemotherapy combinations for which no data were provided on potential drug-drug interactions between Erbitux (cetuximab) and cisplatin or Erbitux (cetuximab) and carboplatin. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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:

- Assess the known serious risks of infusion reactions, cardiopulmonary arrest, pulmonary toxicity, and dermatologic toxicity caused by drug exposures to be achieved with the US-licensed Erbitux (cetuximab) administered at the recommended dose and schedule for this new indication.

- Identify the unexpected serious risks from drug-drug interactions between Erbitux (cetuximab) and cisplatin or Erbitux (cetuximab) and carboplatin.

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 these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to address the serious risks.

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

#1. To compare the safety profiles of U.S.-licensed Erbitux (manufactured by ImClone) and cetuximab (manufactured by Boehringer Ingelheim) you will complete the agreed upon trial, Study I4E-MC-JXBD.

The timetable you submitted on August 18, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date: February 2013
Final Report Submission: February 2014

#2. To determine the potential for pharmacokinetic interactions between Erbitux (cetuximab) and cisplatin you will conduct the drug-drug interaction clinical trial, Study I4E-MC-JXBA.

The timetable you submitted on August 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission Date: December 2011
Trial Completion Date: September 2016
Final Report Submission: November 2016

#3. To determine the potential for pharmacokinetic interactions between Erbitux (cetuximab) and carboplatin you will conduct the drug-drug interaction clinical trial, Study I4E-MC-JXBB.

The timetable you submitted on August 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission Date: December 2011

Trial Completion Date:	December 2016
Final Report Submission:	March 2017

Submit the protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. 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 601.70 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 601.70 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 601.70. 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(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 Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,

/Patricia Keegan/
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