CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

DATE: February 12, 2004

FROM: Sharon Sickafuse SKS
Regulatory Project Manager
Division of Review Management and Policy, HFM-588
Office of Drug Evaluation VI

TO: STN 125084/0

SUBJECT: SBA Equivalent for
Cetuximab
ImClone Systems, Incorporated
U.S. license number 1695

Indications and Usage

ERBITUX, 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.

ERBITUX 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.

Dosage Form, Route of Administration, and Recommended Dosage

ERBITUX, for intravenous (IV) administration, is a sterile, clear, colorless liquid of pH 7.0 to 7.4, usually containing a small amount of easily visible white amorphous Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2.0 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

The recommended dose of ERBITUX in combination with irinotecan or as monotherapy is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended.

Basis for Approval

The following reviews, filed in the CDER correspondence section of the license file for STN 125084/0, comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
CMC (Product, Facility, etc.)	Chana Fuchs, Ph.D. Wendy Weinberg, Ph.D. (1 document for both reviewers)	2-10-04 2-12-04
Clinical (Safety and Efficacy)	Lee Pai-Scherf, M.D. Mark Thornton, M.D. Mary Andrich (1 document for all 3 reviewers)	
Non clinical Pharm/Tox	Anne Pilaro, Ph.D.	2-11-04
Clinical Pharmacology	Hong Zhao, M.D.	2-4-04
Biostatistical	Clare Gnecco, Ph.D.	1-22-04
Bioresearch Monitoring	Jose Tavarez-Pagan	1-14-04
Facilities	Deborah Trout	1-25-04
	Marlene Swider	2-12-04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 2004

FROM: Patricia Keegan, M.D. /S/
Division Director
Division of Therapeutic Biological Oncology Products

SUBJECT: Recommendation for Approval Action on BLA STN 125084 for ERBITUX (cetuximab), to be used in combination with irinotecan, in the treatment of EGFr-expressing metastatic carcinoma in patients who are refractory to irinotecan based chemotherapy.

TO: STN 125084.0

Introduction

ERBITUX™ (Cetuximab) is a chimeric anti-EGFr monoclonal antibody, which binds with high specificity and affinity to the extra cellular domain of the human EGFr. The clinical development of ERBITUX was conducted under BB-IND 5804, which was submitted to FDA on October 18, 1994. In 2000 and 2001, a series of meetings and teleconferences were held between ImClone Systems, Inc and the Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, CBER to discuss the clinical development plan of ERBITUX™ for the treatment of colorectal cancer and the adequacy of the single arm trial, IMCL-CP-02-9923, to support accelerated approval for the treatment of refractory, metastatic colorectal cancer.

On January 12, 2001, ERBITUX™ was granted fast-track designation for the development plan that included the investigation of ERBITUX™ in combination with irinotecan for its effects on durable tumor responses in patients with metastatic colon cancer who are refractory to standard

chemotherapy, where refractory is defined as progressive disease during at least 2 cycles of standard doses of 5-FU and irinotecan. Imclone also requested, and was granted, approval for submission of a rolling Biologics License Application (BLA). The last component of this application, BLA STN 125033.0.0, was the clinical study data, which was submitted on October 31, 2001. The efficacy data were derived primarily from two single arm studies: IMCL-CP-02-9923 (single arm study of cetuximab plus irinotecan in patients with irinotecan refractory metastatic colorectal cancer, n=139) and IMCL-CP-0141 (single arm study of cetuximab alone in patients metastatic colorectal cancer patients who had progressive disease after irinotecan, n=57). Response rate was the primary endpoint for both trials.

The review team identified several major clinical and scientific deficiencies, including but not limited to evidence of deviations from Good Clinical Practices and the critical elements of the clinical protocols, missing data and inconsistencies in reported data for both efficacy and adverse events, lack of data organization, inadequate justification for the proposed dose and schedule, and inadequate justification for the use of irinotecan in combination with cetuximab. Among 196 patients enrolled in the two studies, only 102 (74 enrolled in IMCL-CP-02-9923 and 28 enrolled in IMCL-CP-0141) appeared to meet the population defined in the fast track designation development program. Even in this subpopulation (fast-track), there were substantial amounts of missing data related to both safety and efficacy endpoints. In addition, there was considerable overlap in the confidence intervals around the observed response rates, such that no conclusions could be made as to the value of the addition of irinotecan, a toxic chemotherapeutic agent, i.e., whether outcome in the combination arm was improved over ERBITUX alone. The totality of the deficiencies rendered the application unacceptable for filing and a Refuse to File letter was issued on December 28, 2001.

On February 26, 2002 a meeting was held between FDA, ImClone Systems Inc. and its corporate partners, Bristol-Myers Squibb and Merck KGaA regarding the issues relating to the December 28, 2001 Refusal to File letter and possible pathway for a resubmission of the BLA. Prior to the meeting, ImClone disclosed to FDA that its corporate partner Merck KGaA was conducting a randomized trial in Europe, enrolling over 300 patients with EGFr-expressing, metastatic colorectal cancers which was refractory to irinotecan. Patients in this trial were allocated to treatment with cetuximab plus irinotecan or to cetuximab alone, thus allowing a valid manner to isolate and characterize the contribution of irinotecan to cetuximab therapy. Between February 2002 and June 2003 several meetings were held to provide guidance and reach an agreement

regarding the content and format of a BLA re-submission. On June 5th, 2003, a pre-BLA meeting has held between FDA, ImClone Systems and its corporate partners, Bristol-Myers Squibb and Merck KgaA to reach agreement on the content and format of clinical and pre-clinical data to be submitted in the BLA and on July 31, 2003, a teleconference was held between FDA, ImClone Systems and its corporate partners, Bristol-Myers Squibb to reach agreement on the content and format of chemistry, manufacturing and controls information and facilities information to be submitted in the BLA.

The BLA (STN 125084.0) was resubmitted in a single unit on August 14, 2003 and filed on October 10, 2003. Additional data submitted to the BLA during the review period include:

- Sept. 17, 2003: Safety update, including clinical data from 111 patients enrolled in Study IMCL CP02-0144
- November 12, 2003: Response to item #1 of Oct. 27, 2003 74-day deficiency letter
- December 1, 2003: Responses to items #2-7 of Oct. 27, 2003 74-day deficiency letter
- Jan. 26, 2003: withdrawal of information related to BB36 manufacturing facility
- Feb. 3, 2004: Final draft carton & vial labeling
- Feb. 6, 2004: final draft package insert; clinical & product PMCs with timelines

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Chemistry, Manufacturing, and Controls

See Dr. Chana Fuchs' detailed review

ERBITUX (cetuximab) is a human/mouse chimeric monoclonal antibody of the IgG1 subclass that binds with high affinity to the human epidermal growth factor receptor (EGFr). It is composed of ——— chains, — identical heavy chains ——— ——— identical light chains ——— The antibody chains contain the functional binding domain of murine antibody M225. ———

ERBITUX is provided in single-use vials at a concentration of 2.0 mg/mL and is formulated in a preservative-free solution containing 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, 8.48 mg/mL sodium chloride and Water for Injection, USP.

The cetuximab manufacturing process has been scaled-up and improved over the period of clinical development. Adjustments to the ——— processes have increased

the product yield and process throughput. Cetuximab produced by the various manufacturing processes were determined to be comparable and the comparability studies were found to be appropriate for the stage of development at which the comparability studies were executed. During the review, FDA and Imclone reached agreement on adjustment to some assays or specifications used for lot release of cetuximab drug substance and drug product. Lot release and stability data from drug substance and drug product lots released prior to specification changes have been re-evaluated and confirmed to meet the new specifications as contained in the amendment to the BLA submitted on February 3, 2004. All deficiencies identified on the form FDA 483 issued during the pre-approval facilities inspections have been adequately addressed.

Two issues were identified that will be addressed with further information to be provided under agreed upon post-marketing commitments (PMC).

The current reference standard was found to be acceptable, however FDA and Imclone agreed to adjustment of acceptance criteria for reference standards, to reflect the historical variability, as defined in the improvements in the amendment to the BLA submitted on February 3, 2004. The agreed-upon PMCs are:

1. To set quantitative limits for Cetuximab carbohydrate composition prior to qualification of the next Cetuximab reference standard.

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

Visible aggregates identified as Cetuximab in composition, are normally seen in drug product. Filtration studies have shown that visible aggregates are removed by the in-line filter without significantly affecting the dose received by the patient or clogging the filter.

3. To conduct studies showing 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.

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

5. 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.

Pharmacology/Toxicology

See Dr. Anne Pilaro's detailed review

General Toxicology

The epidermal growth factor receptor (EGFr) is constitutively expressed in many normal epithelial tissues. Tissue binding studies demonstrated that cetuximab bound to surface epithelial growth factor receptor (EGFr) present in the skin, tongue, mammary and salivary glands, ovaries, placenta, and urinary bladder of cynomolgus monkey and human tissues. ERBITUX was evaluated for pharmacologic activity in human tumor xenografts in nude mice and for pharmacokinetics in rats, mice, and cynomolgus monkeys. Tissue binding studies indicated that the cynomolgus monkey was the most relevant species for toxicology studies.

Severe toxicities related to ERBITUX™ were observed in cynomolgus monkeys, following repeated weekly infusion of 7.5, 24, and 75 mg/kg/dose, i/v for up to 39 weeks; these doses represent approximately 0.4 to 4 times the labeled dose of cetuximab, when adjusted for total body surface area. Toxicities in this study included decreases in body weights, food consumption, anemia, decreases in leukocytes and platelet counts, alterations in menstrual cyclicity in the female animals, dose-related elevations in ALT, GLDH, and gamma-glutamyl transpeptidase, and dose-dependent dermatological toxicities. These findings occurred at all dose levels of cetuximab, and were only partially reversible following interruption or discontinuation of dosing, so that no NOAEL could be defined for this ERBITUX in the preclinical safety program.

Early mortality occurred in 5/10 monkeys that were treated with 75 mg/kg/week cetuximab beginning after approximately 12 weeks on treatment, and resulting in early discontinuation of

dosing in this group after 36 weeks on study. Mortality in the high dose animals were related to excessive dermatologic toxicity of ERBITUX following inhibition of the EGFr by cetuximab, and the subsequent defect in maturation of epidermal cells. Prior to deaths in these animals, hyper- and parakeratosis, acanthosis and acantholysis resulting in ulcerative dermatitis with desquamation of the external integuement, and the epithelial mucosa of the nasal passage, esophagus, and tongue, were observed. Secondary bacterial infections of the affected skin resulted in erosive to ulcerative dermatitis, with subsequent septicemia, involvement of the major organs, and death. The dose of ERBITUX at which these early mortalities occurred was approximately 4 times greater than the clinical dose, when scaled by total body surface area.

Clinical toxicities not predicted by the animal studies included severe infusion reactions and interstitial lung disease.

Based on the finding of fatal dose-related mucocutaneous toxicities observed in the cynomolgus monkey study, as well as similar, though uncommon severe cutaneous toxicity complicated by sepsis in the human clinical studies, FDA recommended the addition of this information, including the animal studies, to the WARNINGS section of the package insert.

Toxicology Studies Relating to Fertility and Reproduction

A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of ERBITUX (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6 week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between ERBITUX-treated and control male monkeys.

Animal reproduction studies have not been conducted with ERBITUX. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has the potential to be transmitted from the mother to the developing fetus.

The animal studies assessing the impact of ERTIBUX on fertility and of the potential impact on reproduction are included in the package insert. ERBITUX is approved for use in a patient population with refractory colorectal cancer, following several prior chemotherapeutic regimens. This population is one that is likely to be infertile due to prior treatment. Furthermore, the benefits of ERBITUX (tumor responses) outweighed the risks of impaired fertility and the burden of contraceptive use, if required. However, given that ERBITUX is a likely candidate for treatment in earlier stage disease, particularly as adjuvant treatment, further evaluation of the risks are needed to appropriately guide future studies and counsel patients. Therefore, the following post-marketing commitment was agreed upon between FDA and the applicant:

1. 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.

Data supporting the use of a EFGr tumor expression as an aid in selection of patients for treatment with ERBITUX (see EFFICACY; Relationship between level of EGFR expression and efficacy & Data supporting the use of a EFGr tumor expression as an aid in selection of patients for treatment with ERBITUX, page 14)

Clinical Pharmacology

See Dr. Hong Zhao's detailed review.

Pharmacokinetics were evaluated when ERBITUX™ was administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy. The pharmacokinetic behavior of cetuximab together with its pharmacodynamic activity on the EGFr was found to be supportive of both the recommend dose and schedule.

Pharmacokinetic Analysis by Site of Product Manufacture

The dataset for the population pharmacokinetic (PK) analysis were derived from clinical studies that utilized different lots of ERBITUX. The PK profile (primarily peak and trough levels) obtained with different lots produced by different manufacturing processes from the Lonza contract manufacturing facilities was similar and the site of manufacture and manufacturing process did not appear to influence the resulting pharmacokinetics. However, lots of ERBITUX manufactured in BB36 site, which were not included in the population PK analysis, were shown to be pharmacokinetically noncomparable to clinical lots manufactured in Lonza facility; lots

manufactured at the BB36 site yielded a 26% increase in mean trough concentration and 52% increase in mean peak concentrations as compared to the Lonza-manufactured lots. Lots manufactured at the BB36 site were not used in the major efficacy or supportive studies and a potential detrimental effect on the safety profile (higher incidence of serious adverse events or previously unreported serious adverse events) as a result of increased drug exposure with BB36-manufactured material exists. Information on this manufacturing facility was withdrawn from the BLA; Imclone will submit data on this facility along the safety data from a 250-patient study of ERBITUX monotherapy (IMCL-CP02-0144) to show that the increased exposure with the BB36-manufactured material does not substantially alter the safety profile (either in general incidence or severity). A detrimental effect on anti-tumor efficacy is not expected as a result of the increased exposure.

CLINICAL

Efficacy Data

The demonstration of efficacy in this application is based on the surrogate endpoint of durable objective responses in patients with irinotecan-refractory metastatic colorectal with no effective alternative therapy in three clinical trials enrolling 524 patients. The response rates observed following cetuximab alone and in combination with irinotecan were clinically important and durable. The added toxicity of irinotecan is offset by the statistically significant improvement in tumor response and time to tumor progression for cetuximab when used in combination with irinotecan in comparison to cetuximab alone in irinotecan-refractory patients. However, the activity of cetuximab alone is sufficient to justify approval for use in patients whose tumors are no longer responding to existing therapies and are unable to tolerate irinotecan.

Study Protocol EMR 62202-007 is a multicenter, open label, randomized Phase II study of cetuximab alone or in combination with irinotecan in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFr) and progressing on a defined irinotecan-based regimen.

EMR 62202-007 is a well-conducted, randomized phase 2 trial in a refractory, metastatic colorectal patient population who had progressed after first line therapy. In addition to having failed 5-Fluouracil and irinotecan, 38% of the patients (124/329) were refractory to oxaliplatin. There are no existing therapies for this latter patient population. The study arms were well-

balanced for baseline entry characteristics. Characteristics of the patient population, by treatment arm, are presented in the table below:

Baseline Entry Characteristics by Treatment Arm in EMR 62202-007		
Characteristics	ERBITUX plus irinotecan (N=218)	ERBITUX Monotherapy (N=111)
Site of primary:		
Colon	125 (57.3)	65 (58.6)
Rectum	90 (41.3)	43 (38.7)
Missing	3 (1.4)	3 (2.7)
Karnofsky Performance Status		
< 80	26 (11.9%)	14 (12.6%)
≥ 80	192 (88.1%)	97 (87.4%)
No. Metastatic sites		
1	102 (46.8%)	62 (55.9%)
2	78 (35.8%)	27 (24.3%)
> 2	9 (4.1%)	6 (5.4%)
Tumor sites		
Liver	153 (70.2%)	76 (68.5%)
Lung/Lymph node chest	71 (32.6%)	29 (26.1%)
Lymph node abdomen/pelvis	21 (9.6%)	16 (14.4%)
Intestine/visceral	3 (1.4%)	0 (0%)
Other	38 (17.4%)	13 (11.7%)
No. Previous Rx lines		
1	41 (18.8%)	27 (24.3%)
2	79 (36.2%)	41 (36.9%)
3	61 (28.0%)	20 (18.0%)
>3	37 (17.0%)	23 (20.7%)
Adjuvant therapy	59 (27.1%)	37 (33.3%)
Prior oxaliplatin	135 (61.9%)	71 (64.0%)

The assessments of response rate and response duration, as reported below, were determined by an independent response evaluation committee that was masked to treatment and to the investigator's assessment of response. Response rates were assessed in the following populations

1. **Intent to treat (ITT)**: All randomized patients
2. **Per protocol:** All IRC-PD patients who did not had a major protocol violation, had adequate study medication compliance, i.e., received at least 50% of the scheduled cetuximab treatment (number of infusions divided by weeks of cetuximab treatment) > 0.5, had received at least 6 weeks of cetuximab treatment, except in case of death or PD within the first 6 weeks after start of cetuximab treatment.
3. **IRC PD:** All ITT patients with an objective confirmed irinotecan-refractory status:
   - Progressed on prior irinotecan as determined by the IRC
   - Progressed within 30 days after the last irinotecan treatment course, i.e., pre-study scans documenting progressive disease

- For the 125 mg/m^2 weekly and for the 350 mg/m^2 every 3 weeks schedule: within 51 days of last dose of prior irinotecan
- For the 180 mg/m^2 every 2 weeks schedule within 44 days of last dose of prior irinotecan

- Pre-study comparison scan was performed either less than or equal to 6 weeks (42 days) prior to the first dose of the most recent irinotecan therapy or performed after first dose, at least four weeks prior to the date of the scan used to assess progression
- Pre-study comparison scan/pre-study scan documenting PD: at least a 4- week interval between the 2 scans covering at least 1 course (cycle) of irinotecan therapy
- Minimum irinotecan dosing: received adequate pre-study irinotecan
- Received any dose of cetuximab

4. **ITT oxaliplatin:** All ITT patients with prior oxaliplatin therapy
5. **IRC PD oxaliplatin:** All IRC-PD patients with prior oxaliplatin therapy

Two additional subpopulations were also analyzed, at the recommendation of the FDA, in support of the BLA re-submission:

1. **IRC PD oxaliplatin-failure population:** all IRC-PD patients where the reason for failure of oxaliplatin treatment is either disease progression or intolerance.
2. **IRC PD-2cycle:** All IRCPD patients who had received a minimum of 2 cycles of irinotecan-based therapy. The IRC PD-2 cycle subpopulation meets the FDA criteria for Fast Track Designation for ERBITUX (January 12, 2001)

The objective tumor response rates as determined by the IRC were confirmed by review of radiographs and case report forms by FDA review staff. The overall response rates in the intent-to-treat population were 22.9% and 10.8% in the ERBITUX plus irinotecan (combination) and ERBITUX monotherapy arms, respectively. The difference in response rates between the between the combination and monotherapy arms was statistically significant (p=0.0074), favoring the combination arm. The responses observed in both treatment arms were durable; the median durations of response were 5.7 months and 4.2 months in the combination and monotherapy arms, respectively. A statistically significant longer time to progression was observed in the combination as compared to the monotherapy arm (median 4.1 months vs. 1.5 months, $p < 0.0001$).

The overall response rates for combination therapy arm in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory (23.8%) subpopulations were similar to that observed for the combination arm in the ITT population (22.9%). The overall response rates in the monotherapy arm for the IRC-PD (11.3%) and IRC-PD oxaliplatin failure (12.4%) subpopulations were also similar to that observed for the ERBITUX monotherapy in the ITT population (12.1%). The study was not powered to detect statistically significant difference in response rates between the combination and monotherapy treatment arms for any of the subpopulations of interest.

Objective Response Rates in the ITT Population and in Subpopulations of Interest in EMR 62202-007

Population	ERBITUX plus irinotecan		ERBITUX monotherapy		Asymptomatic	
	n/N	%	n/N	%	% 95% CI	P-value*
ITT	**50/218**	**22.9**	**12/111**	**10.8**	**12.1**	**0.0074**
ITT oxaliplatin	30/135	22.2	6/71	8.5	13.8 (4.2, 23.3)	0.0127
Per protocol	34/122	27.0	10/66	15.2	12.7 (1.0, 24.5)	0.0702
IRC-PD	34/135	25.2	10/71	14.1	11.1 (0.2 22.0)	0.0747
IRC-PD oxaliplatin	21/84	25.0	5/46	10.9	14.1 1.2, 27.0	0.0673
IRC-PD oxaliplatin failure	19/80	23.8	5/44	11.4	12.4 (-0.8, 25.6)	0.104
IRC-PD 2 cycles	34/132	25.8	10/69	14.5	11.3 (0.1, 22.4)	0.074

* Value for difference in proportions between groups obtained by Fisher's exact test (2-tailed)

In a series of exploratory analyses, response rates were generally similar regardless of the number of prior treatment lines, regardless of prior oxaliplatin treatment and across all irinotecan schedules used. Although the observed response rate was lower in patients who received 125 mg/m^2 weekly irinotecan as compared patients receiving other schedules, due to the exploratory nature of the analysis and the small number of patients, it is inappropriate to draw conclusions about relative efficacy and the results are deemed only descriptive.

Duration of Response in the ITT and subpopulations in EMR 62202-007

Population	ERBITUX plus Irinotecan Months (CI 95%)	ERBITUX monotherapy months (CI 95%)
ITT	5.7 (4.2, 7.6)	3.2 (2.8, 5.5)
• IRC-PD	4.2 (3.8, 7.3)	4.1 (2.8, 5.5)
• IRC-PD oxaliplatin failure	5.6 (4.2, 7.3)	4.2 (2.7, 6.5)
• IRC-PD 2 cycle	4.2 (3.8, 7.3)	4.1 (2.8, 5.5)

Time to Progression (per IRC) in ITT and subpopulations in EMR 6202-007				
Populations	Median TTP: ERBITUX + Irinotecan	Median TTP: ERBITUX Monotherapy	Hazard Ratio (95% CI)	Log-rank p-value
ITT	4.1 mo	1.5 mo	0.54 (0.42, 0.71)	<0.001
• IRC-PD Oxaliplatin failure	2.9 mo	1.5 mo	0.48 (0.31, 0.72)	<0.001
• IRC-PD 2 cycle	4.0 mo	1.5 mo	0.52 (0.37, 0.73)	<0.001

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Study Protocol IMCL CP02-9923 is a multicenter, open label, non-randomized Phase II of cetuximab in combination with irinotecan therapy in patients with advanced colorectal carcinoma who had progressive disease after irinotecan-containing therapy.

Study IMCL-CP02-9923 included 138 patients with EGFr expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen. Patients received ERBITUX™ plus the same dose and schedule of irinotecan as the patient had previously failed. Of 138 patients enrolled, 83 patients had documented progression to irinotecan as determined by an Independent Review Committee. The irinotecan progression criteria were less stringent than that proposed for EMR-6202-007 study, as patients were not required to have failed within 30 days of prior irinotecan therapy. In addition, collection of data confirming prior irinotecan failure was performed retrospectively, rather than prospectively. There were a significant number of protocol violations in this trial; these included: no evidence of metastatic colorectal disease at baseline, a lack of measurable disease at baseline, the most recent prestudy irinotecan dose was 25mg/m^2 less than the first on-study dose for the weekly irinotecan schedule (or < 50mg/m^2 for an every 3 week irinotecan schedule), and no evidence of positive EGFr expression. Nine patients in the IRCPD cohort (10.8%) and 12 patients in all treated patients population (8.7%) had major violations. Patients with major protocol violations were excluded in subpopulation analyses for response rate and duration.

The overall response rate, confirmed by FDA analysis, was 15.2 % (21/138) for the all-treated population and 12.1 % (9/74) for the irinotecan failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ITT	21/138	15.2%	9.7% 22.3%
IRC-PD	11/83	13.3%	6.8%, 22.5
IRC-PD per protocol	9/74	12.1%	5/7%, 21/8%
IRC PD-2 cycles	6/46	13.0%	4.9%, 26.3%

Study Protocol IMCL-CP02-0141 is a multicenter, open label, multiple-dose, uncontrolled, Phase II study of cetuximab alone in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFr) and progressing on a defined irinotecan-based regimen.

Study IMCL-CP02-0141 included 57 patients with EGFr expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Radiographic documentation of progression to irinotecan was not required for this study. Of 57 patients enrolled, 28 patients had documented history of progression to prior irinotecan regimen. The overall response rate, confirmed by the FDA analysis was 8.8 % (5/57) for all treated patients and 14.3% (4/28) for the irinotecan failure group. No complete responses were observed. The median duration of response was 4.2 months for both groups.

ITT	5/57	8.8%	2.9%, 19.3%
IRC-PD	4/28	13.3%	6.8%, 22.5

Summary of Effectiveness and Confirmatory Studies Required

The effectiveness of ERBITUX is based on durable, objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX. Granting of accelerated approval is contingent upon completion of clinical studies to verify the clinical benefit of ERBITUX. The following post-marketing commitments are required as set out in 21 CFR 601.41. Both studies are ongoing.

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.

Special Considerations in Review of Efficacy

Relationship Between Presence/Severity of Cutaneous Toxicity and Efficacy

The applicant performed an exploratory analysis of response rate as a function of the presence and severity of skin toxicity in the proposed package insert. In support of inclusion of information in the proposed package insert, the applicant presented the following analyses of response rate as a function of the presence of cutaneous toxicity.

Response rate as a function of skin toxicity in EMR 62202-007 (ITT population)				
Prior therapy	[redacted]		[redacted]	
	N/N (%)	95% CI	N/N (%)	95% CI
Acneform rash				
None	8/48 (16.7)	7.5, 30.2	2/27 (7.4)	0.9, 24.3
Any	31/170 (24.7)	18.4, 31.9	10/84 (11.9)	5.9, 20.8
Grade 3	13/22 (58.1)	36.4, 79.3	1/4 (25.0)	0.6, 80.6
Skin reaction				
None	2/32 (6.3)	0.8, 20.8	0/18 (0)	0.0, 18.5
Any	48/186 (25.8)	19.7, 32.7	12/93 (12.9)	6.8, 21.5
Grade 3	16/29 (55.2)	35.7, 73.6	2/6 (33.3)	4.3, 77.7

Much speculation has arisen in the medical community regarding the potential for cutaneous toxicity as a predictor of response and as a potential guide for optimal dosing for EGFr-targeted products; i.e., that responses rates are higher in patients with more severe skin reaction (vs. no or less severe reactions). The implications, as suggested by investigators participating in this study,

is that a dose which yields cutaneous toxicity is more effective and the more severe the cutaneous toxicity, the more effective. The FDA does not find that there is sufficient data to suggest such a relationship between cutaneous toxicity and likelihood of response exists based on the post-hoc exploratory nature of the analysis, the small numbers of patients in each subgroup [particularly in the Grade 0 and Grade 3 categories], and the lack of correlation between pharmacodynamic effects in the skin and tumor within individual subjects (see Dr. Hong Zhao's detailed review).

Cutaneous toxicity is a dose-related adverse event and was among the dose-limiting toxicities observed at a dose of 500mg /m^2. Cutaneous toxicity, particularly in the more severe forms, can be associated with serious morbidity, including sepsis. Morbidity and mortality associated with severe cutaneous toxicity was observed in animal toxicology studies conducted in cynomolgus monkeys (see Pharmacology/Toxicology review section). FDA also notes that the pharmacokinetic and pharmacodynamic relationships do not support the results of the exploratory analysis. The relevant pharmacologic findings are summarized:

- The pharmacodynamic effects of a single dose of cetuximab on signal transduction and cell markers in skin and tumor tissues were variable and inconclusive. There were no discernible correlations between pharmacodynamic effects in skin and tumor tissue.
- The potential relationship between cetuximab exposure and the EGFr status or the response was explored in patients who had colorectal cancer and received the targeted ERBITUX dose. The derived intrinsic clearance from the saturable elimination pathway was used as a surrogate for exposure. Visual inspection of the data revealed no relationship between those patients considered to have responded and those that did not and their exposure to cetuximab. Accounting for difference in cetuximab exposure by gender gave similar results. Skin rash (a major adverse event) was included, as a potential covariate (categorical variable) in the population PK analysis and there appeared to be no discernible relationship between skin rash and cetuximab systemic exposure.

An analysis assessing for the incidence of rash among responding and non-responding patients, conducted by FDA and presented in the following table.

INCIDENCE OF CUTANEOUS TOXICITY AS A FUNCTION OF RESPONSE STATUS IN EMR 62202-007 (ITT Population)				
	ERBITUX PLUS IRINOTECAN (N=218)		ERBITUX MONOTHERAPY (N=111)	
Acneform rash	Responder n=50(%)	Non-Responder n=168(%)	Responder n=12(%)	Non-Responder n=99(%)
None	8 (16.0)	40 (23.8)	2 (16.6)	25 (25.2)
Grade 1-2	29 (58.0)	119 (70.8)	9 (75.0)	71 (71.7)
Grade 3	13 (26.0)	9 (5.3)	1 (8.3)	3 (3.0)

As can be seen, the incidence of any toxicity and of severe cutaneous toxicity, was similar in responders and non-responders. Mild-to moderate cutaneous toxicity occurred in the majority of patients, both those patients who responded and those who did not, while lack of cutaneous toxicity and severe toxicity were seen in a minority of patients regardless of response status. Importantly, 16% and 17% of the responders in the combined and monotherapy arms, respectively, experienced no cutaneous toxicity.

Given the morbidity associated with more severe cutaneous toxicity, including sepsis, and the increased morbidity and mortality observed in non-human primates who experience severe mucocutaneous toxicity, the relative safety and effectiveness of a dosing strategy that targets mild to moderate skin toxicity (as compared to the approved dose and schedule) should be established in clinical trials prior to general implementation. This should preferably be done in a randomized trial comparing the two dosing regimens. The applicant has initiated a single arm study, titled Protocol CA225045, "An Exploratory Pharmacogenomic Study of Cetuximab Monotherapy in Patients with Metastatic EGFr-positive Colorectal Carcinoma" which will provide information regarding the safety of a dosing strategy targeted to achieve mild-moderate cutaneous toxicity.

Relationship between level of EGFR expression and efficacy & Data supporting the use of a EFGr tumor expression as an aid in selection of patients for treatment with ERBITUX

ERBITUX binds to the EGFr with an affinity that is approximately 5 to 10-fold higher than that of endogenous ligands (epidermal growth factor and transforming growth factor-alpha). *In vitro* assays and *in vivo* animal studies have shown that ERBITUX, alone or in combination with irinotecan, 5-fluorouracil, or cisplatin chemotherapy inhibits the growth and survival of human

tumor cells that over-express the EGFr. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFr expression. All studies under the clinical development program were restricted to patients whose tumors expressed EGFr (75-82% of the patients screened in the three studies supporting efficacy had EGFr-expressing tumors according to the EGFR pharmDx™ manufactured by DakoCytomation).

FDA conducted exploratory analyses assessing the relationship between EGFR expression and objective tumor response. In the population analyzed, neither the percentage of EGFr positive cells nor the EGFr staining on the tumor cells correlate with response rate.

Response rate as a function of EGFr expression in EMR-6202-007 (ITT population)				
EGFr expression	**ERBITUX plus irinotecan**		**ERBITUX monotherapy**	
	n/N (%)	95% CI	n/N (%)	95% CI
EGFr % positive cells				
0 to ≤ 10%	15/109 (**22.9**)	15.4, 32.0	4/56 (**7.1**)	2.0, 17.3
>10 to ≤ 20%	4/20 (**20.0**)	5.7, 43.7	5/16 (**31.3**)	11.0, 57.7
20 to ≤ 35%	6/27 (**22.2**)	8.6, 42.3	0/7 (**0.0**)	0.0, 41.0
> 35%	15/62 (**24.2**)	14.2, 36.7	3/32 (**9.4**)	2.0, 25.0
EGFr staining				
Faint/barely	11/53 (**20.8**)	10.8, 34.1	1/21 (**4.8**)	0.1, 23.8
Weak to moderate	22/89 (**24.7**)	16.2, 35.0	7/55 (**12.7**)	5.3, 24.5
Strong	17/75 (**22.7**)	13.8, 33.8	4/34 (**11.8**)	3.3, 27.5

Although clinical studies did not enroll patients whose tumors were EGFr negative, the proposed mechanism of action of cetuximab and the non-clinical data showing lack of effectiveness in tumors lacking EGFr expression supports the use of a test for EGFr expression in tumor to select patients who are most likely to benefit from ERBITUX. However to confirm that efficacy is restricted to patients whose tumors express the EGFr or that efficacy is greater in patients whose tumors EGFr expression, such that a test identifying EGFr is useful in selection of patients for whom ERBITUX is indicated, the following post-marketing commitment was agreed upon between FDA and the applicant:

1. 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.

2. 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.

DSI – Inspectional Findings

See Mr. Tavarez-Pagan's review for full details.

FDA's Division of Scientific Investigation (DSI) audited selected centers to assess data quality and integrity. Sites that accrued the largest number of patients were selected for DSI audit. There were four clinical sites inspected for Study EMR 62202-007, two in Brussel, one in Italy and one in France. These sites accrued 111 of the 329 patients enrolled in this study. All deviations noted at these sites were minor and DSI determined that study conduct and data quality from these sites were acceptable. In addition, DSI conducted inspections of four clinical sites participating in Study IMCL-CP02-9923 and one clinical site participating in Study IMCL-CP02-0141. These sites accounted for 51 of the 139 patients enrolled in Study IMCL-CP02-9923 and 12 of 57 patients enrolled in Study IMCL-CP02-0141. DSI determined that general study conduct and data quality from these sites were acceptable, i.e., the BLA information accurately reflected the primary source documents. FDA 483 forms recommending voluntary corrective action were issued to 2/4, 2/4 and 1/1 sites inspected for EMR 62202-007, IMCL-CP02-9923 and IMCL-CP02-0141, respectively.

Safety

General

More than 1100 cancer patients were treated with cetuximab during the clinical development program. Clinical information from 911 patients enrolled in Phase 2 studies was used to assess the overall toxicity profile of cetuximab; this was supplemented by data from Phase 1 studies, studies conducted outside of the IND (in Europe), and studies conducted with product from an alternate manufacturing site in order to characterize unusual and serious adverse events. In the Phase 2 studies, treatment with cetuximab was either as a single agent, or in combination with chemotherapy or radiation therapy. The majority of patients in the safety database had colorectal cancer. The chemotherapeutic agent most commonly administered in combination with cetuximab was irinotecan.

Except where indicated, the data described below reflect exposure to ERBITUX in 633 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=279) across four studies. These studies were EMR 62202-007, IMCL CP02-9923, IMCL CP02-0141, and the interim safety data from an ongoing study of ERBITUX monotherapy (IMCL CP02-0144) being conducted with product manufactured at the BB36 (Branchburg, NJ) facility. Patients receiving ERBITUX plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving ERBITUX monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most serious adverse reactions observed in clinical trials of ERBITUX, alone or in combination with irinotecan, were infusion reactions (3%), dermatologic toxicity (1%), interstitial lung disease (0.5%), fever (5%), sepsis (3%); renal dysfunction (2%), pulmonary embolism (1%), dehydration (5% in patients receiving ERBITUX plus irinotecan; 2% in patients receiving ERBITUX monotherapy), and diarrhea (6% in patients receiving ERBITUX plus irinotecan, 0% in patients receiving ERBITUX monotherapy). Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 14 (5%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%). The most common adverse events seen in 279 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Cutaneous Toxicity

Acneform-rash skin toxicity was the most common adverse event associated with Cetuximab (approximately 90% of patients). The reaction was described by a variety of terms (acne, rash, pustular rash, dry skin, exfoliative dermatitis, etc.), usually occurred within the first three weeks of therapy. The majority of reactions were mild to moderate in severity (NCI CTC grades 1 and 2). In a minority of patients (12%), NCI CTC grade 3 toxicity was reported. No patient in clinical studies was reported to have NCI CTC grade 4 toxicity. Of those experiencing cutaneous toxicity, skin rash occurred within the first 3 weeks of treatment in approximately 75% of these patients and persisted for at least several weeks. In most patients there was improvement in severe skin reactions with dose reduction or cessation of cetuximab, however even in those patients with improvement, complete resolution of toxicity did not occur prior to death or discontinuation from study. In a small number of patients with severe (Grade 3) skin toxicity developed concomitant *Staph aureus* septicemia and sepsis.

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Additional important information on factors potentially influencing cutaneous toxicity was derived from a study of 21 patients with locally advanced squamous cell cancer of the head and neck. In this study, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port.

The package insert was modified to include data on the potential for additive cutaneous toxicity when ERBITUX and irradiation as administered concurrently. Additional precautions

recommended by the applicant were use of protective clothing and sunscreen to minimize potential additive skin toxicity of ERBITUX and sun exposure. The Dosage and Administration section of the package insert reflects the dose modification criteria used in the clinical studies, for management of cutaneous toxicity. The data from clinical studies indicate that dose reduction resulted in reduction in the severity of toxicity, although complete resolution was frequently not observed while patients remained on treatment.

Infusional Reactions

Patients in the clinical studies were routinely pre-medicated with anti-histamines in clinical studies, despite premedication, approximately 20% (19% of combination therapy and 25% of monotherapy patients) experienced infusion reactions. Infusion reactions, was defined as a symptom-complex including one or more of the following: "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnea", and were most commonly observed with the first dose. Severe infusion reactions were uncommon (3% of all patients) and 90% of severe infusion reactions were observed with the first dose. Treatment of patients with a test dose of Cetuximab was found to not be predictive of occurrence of severe infusion reaction. The utility of antihistamine prophylaxis in ameliorating the severity of infusion reactions has not been studied.

The package insert describes infusion reactions in the Boxed Warnings and Warnings sections. The Dosage and Administration section describes dose modifications (reduction in rate of infusion or termination of infusion) for the management of moderate and severe reactions, respectively. The basis for these recommendations were based on experience in clinical studies indicating that decrease in infusion rate led to improvement adjustments

Pulmonary Toxicity

Pulmonary toxicity in the form of interstitial lung disease was a rare but significant toxicity associated with Cetuximab. Two patients developed interstitial pneumonitis following administration of Cetuximab, and one of the patients died as a result of their ILD. Two patients with pre-existing pulmonary fibrosis experienced a worsening of their disease while receiving Cetuximab in a manner similar to that observed in another EGF receptor / pathway based therapy. Of note, in clinical studies of both combination and monotherapy, the incidence of dyspnea was increased over that expected in this patient population. The incidence of dyspnea of any severity

(NCI CTC grades 1-4) was 22% and of severe dyspnea (NCI CTC grade 3-4) was 4%; a few of these reports represent infusional toxicity.

Chemotherapy-associated Toxicity

Diarrhea and neutropenia in the clinical studies were most often due to concomitant chemotherapy. Addition of Cetuximab did not appear to worsen adverse events associated with chemotherapy, and concomitant chemotherapy treatment did not appear to impact Cetuximab-associated adverse events.

Immunogenicity

Cetuximab is a foreign protein, and as such, has the potential to elicit an immune response in patients. Serologic (humoral) immune responses to cetuximab were assessed using either a double antigen radiometric assay or an ELISA. While the observed incidence of immune responses was low, the inadequate validation information regarding the assays' performance has limited the ability to assess clinical immunogenicity data appropriately. This is reflected in the Erbitux package insert. Additional validation of both assays for accuracy, precision, sensitivity, specificity and robustness is a post marketing commitment. Additionally, assessment of Erbitux immunogenicity using a validated assay is a clinical post-marketing commitment.

1. 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.

2. 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

Special Populations

Population pharmacokinetic analysis identified gender-related difference in pharmacokinetics. Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. Observed response rates were higher in males as compared to females, however given the small number of responses, conclusions cannot be drawn. The toxicity profile observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary.

There were insufficient numbers of patients across different racial groups to assess for ethnic differences in pharmacokinetics. There were small numbers of patients with severe organ dysfunction, however there were patients with various levels of impairment. There was no evidence of altered pharmacokinetics associated with renal or hepatic impairment. Differences in pharmacokinetics in older versus younger patients were not observed, however pediatric patients were not studied. Pediatric patients will be studied as a post-marketing commitment (see below).

1. 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.

Proprietary name review

The proposed proprietary name of ERBITUX was reviewed the Division of Medication Error and Technical Support (DMETS) and found to be acceptable.

RECOMMENDATION

All members of the review team recommended approval for ERBITUX under 21 CFR 601.40-44 for the following indications:

•

- ERBITUX monotherapy is indicated for the treatment of patients with EGFr-expressing metastatic colorectal cancer, which has progressed or recurred after an irinotecan-containing chemotherapy regimen, and who are intolerant to irinotecan.

I concur with the findings of review team and recommend approval for ERBITUX for the indication above.

DEPARTMENT OF HEALTH AND HUMAN SERVICES | Public Health Service

Food and Drug Administration
Center for Drugs Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

Date: October 29, 2003 (Initiated)
February 10, 2004 (Finalized)

To: Administrative File, **STN 125084/0**

From: Marlene G. Swider, Biologist, OCBQ/DMPQ MRB I, HFD-328 MGS 2-12-04

Through: Michael D. Smedley, Branch Chief (Acting), CDER, OC/DMPQ TFRB, HFD-328
MDS 2-12-04

Subject: **Review Memo: Biologic License Application (BLA):** cetuximab (ERBITUX ™), addition of new product to multi-product facility, ImClone Systems, Inc.
US License 1695

Action Due: February 13, 2004.

Recommendation: I recommend approval of this file.

Summary

ImClone Systems, Inc. is submitting this biologic license application (BLA) dated August 12, 2003, to seek licensure for the manufacturing of their new product, cetuximab, (ERBITUX™). The drug substance for cetuximab will be manufactured at the ImClone Systems proposed commercial manufacturing facility in Somerville, New Jersey (BB36), and their Lonza Biologics' commercial manufacturing in Portsmouth, New Hampshire (Lonza facility). Cetuximab drug product will be manufactured at ——————————— Cetuximab is for the treatment of EGFr-expressing colorectal carcinoma in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.

Cetuximab was granted Fast Track Drug Development status on January 12, 2001 for the above-proposed indications in accordance to section 506 of the Food, Drug and Cosmetic Act. ImClone Systems, Inc. has requested that this BLA be granted Priority Review status and FDA has accepted.

This BLA was submitted as a full electronic submission in duplicate in accordance with the 21 CFR Part

11 on two separate digital linear tapes. This BLA was received on August 14, 2003 and its final due date is February 13, 2004.

The review for this BLA includes only the following parts: FDA Form 356h, Cover Letter, Table of Contents, Summary, Chemistry Section with its appendices for establishments description and manufacturing steps.

24 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Conclusion

I. I recommend approval of this supplement based on the facility and manufacturing sections above assigned to me for review during inspection and as included in the EIR and the approval of all the FDA 483 outstanding issues [redacted]

II. I have deferred the review of the following sections to the product office as noted through the content of this review memo:

Product characterization and testing
Stability data
Raw Materials and Reagents
Animal and cellular sources
Batch Records
All amendments to this BLA with the exception of amendment 11 and 14 reviewed by DMPQ

III. [redacted]

Cc: HFD-328, Swider
HFD-328, Smedley
HFM -588, Sickafuse
HFM- 555, Fuchs
[redacted]

Date prepared: Swider; October 29, 2003.
Comments by: Smedley, February 10, 2004.
Revised by: Swider, February 11, 2004.

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: January 12, 2004

To: Chana Fuchs, BLA Committee Chair, CDER, OPS/OBP/DMA, HFM-555

From: Deborah Trout, BLA Committee Member, CBER, OCBQ/DMPQ, HFM-675 1/20/04

Through: Michael D. Smedley, Acting Branch Chief, CDER, OC/DMPQ/TFRB, HFD-328 1/25/04

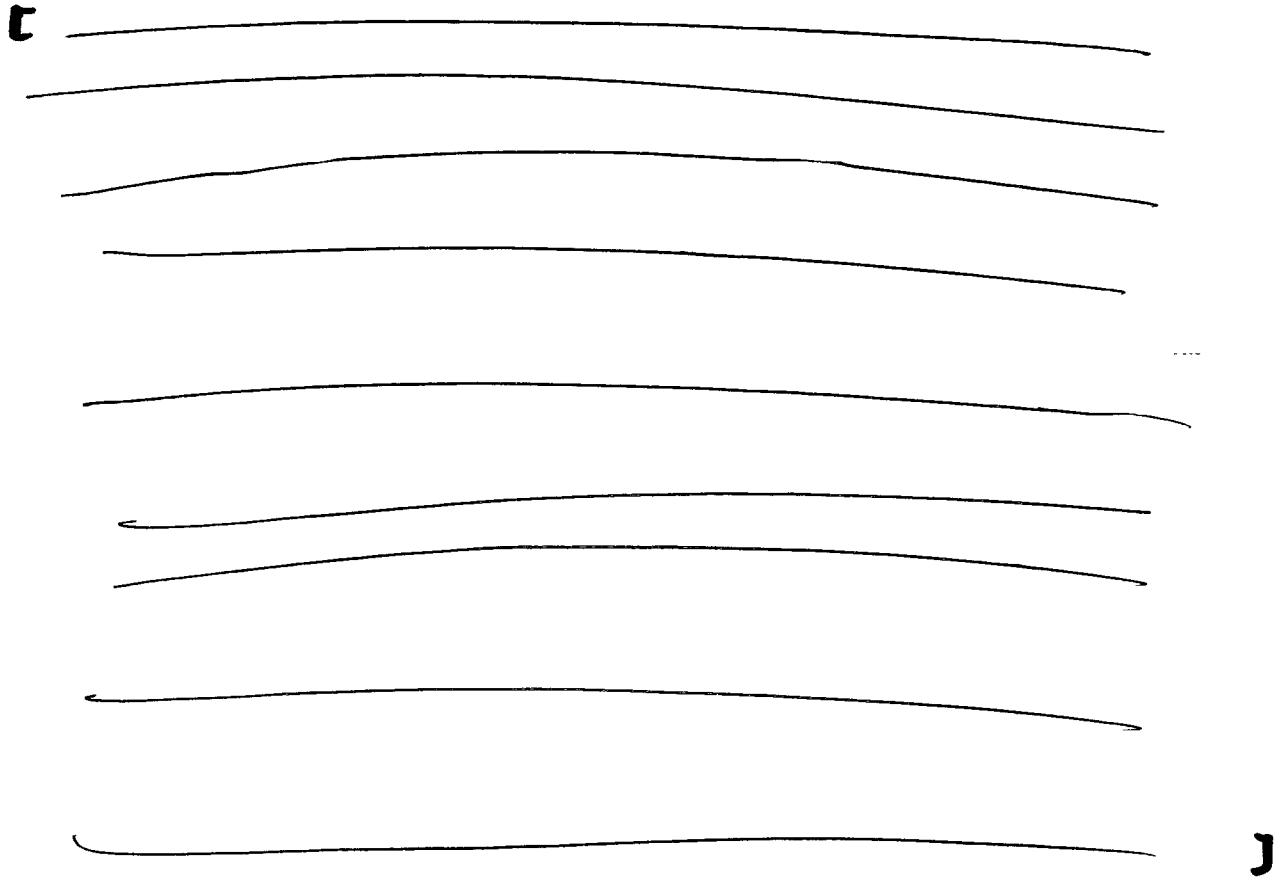
Subject: Review of Biologics License Application (BLA) from ImClone Systems Incorp., for the manufacture, formulation, fill and packaging of ERBITUX™ (Cetuximab); STN Number 125084/0

My review includes an evaluation of the following sections submitted in ImClone's Biologics License Application (reference is made to Table of Contents for Cetuximab BLA in the electron submission): Item 3 Summary (section 2.3 Quality Overall Summary), Item 4 Chemistry, Manufacturing and Controls (sections 3.1 - 3.2, 3.2.S [BB36 and Lonza], 3.2.P , 3.2.A [Appendices], 3.2.R.2 [Methods Validation], Environmental Assessment and 3.2.R.1 [Batch Records]), and Item 15 Establishment Information (sections 3.2.A.1 - 3.2.A.2)

This review memo is divided into 4 main sections followed by page number and date the review was entered into this memorandum:

**Please note that this review memo is comprehensive with respect to the initial review of the application, the inspection and follow-up review regarding inspectional items. The review narrative (section IV) and inspectional issues (section III) related to the Bulk Drug Substance were entered into this memo on 11/04/03. The review narrative (section IV) and inspectional issues (section III) related to the Drug Product were entered into this memo on 11/26/03. This review memo was finaled 1/12/04.

18 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



Prepared by: CBER/OCBQ/DMPQ/D. Trout: 10/23/03, 10/31/03, 11/04/03, 11/26/03, 1/12/04, 1/20/04

cc: Sickafuse Fuchs
Kelley Smedley

15 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.