

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**STN/BLA 125084**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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Brand Name	ERBITUX™
Generic Name	Cetuximab, Chimeric anti-EGFr monoclonal antibody
Reviewer	Hong Zhao
Supervisor	Martin David Green
Branch	Clinical Pharmacology / PharmTox
ODE VI Division	Oncology
Sponsor	ImClone
Relevant IND(s)	BB-IND 5084, BLA 125033/0
Submission Type; Code	NME, Fast Track
Formulation; Strength(s)	Single-use, ready-to-use vials containing a 2 mg/ml solution in phosphate-buffered saline for intravenous administration
Indication	

### **1 Executive Summary**

#### **1.1 Recommendation**

The results of clinical pharmacologic and pharmacokinetic studies support the approval of the clinical trial drug product – ERBITUX manufactured at the Lonza facility. Due to higher systemic exposure of the drug product manufactured at the BB36 facility compared to the clinical trial product, clinical safety should be demonstrated to support its approval.

#### **1.2 Phase IV Commitments**

There are no Phase IV commitments requested from Clinical Pharmacology and Biopharmaceutics perspective. Phase IV commitments from clinical, pharmacology/toxicology and CMC perspectives include confirmatory studies for accelerated approval, additional nonclinical reproductive toxicology study(ies) in a suitable animal species, and a study to characterize the immune response to cetuximab using a validated immunogenicity assay(s).

## 2 Table of Contents

1	Executive Summary .....	1
1.1	Recommendation .....	1
1.2	Phase IV Commitments .....	1
2	Table of Contents .....	2
3	Summary of CPB Findings .....	3
4	QBR.....	6
4.1	General Attributes.....	6
4.2	General Clinical Pharmacology.....	7
4.3	Intrinsic Factors .....	14
4.4	Extrinsic Factors .....	17
4.5	General Biopharmaceutics.....	19
4.6	Analytical.....	21
	Reviewer and Supervisor Sign-off Sheet.....	23
5	Recommended Labeling.....	24
6	Appendix .....	41
6.1	Proposed Labeling .....	41
6.2	Individual Study Reviews.....	59
	Product Development Rationale.....	59
	Clinical Pharmacology and Pharmacokinetics Program.....	59
	Pharmacokinetics.....	60
	Dose-Escalation Studies (Single Dose).....	60
	Target -Dose Studies (Multiple Doses).....	65
	Population Pharmacokinetic Evaluation.....	68
	Pharmacokinetics in Special Populations.....	68
	Inter-Individual Variability in PK Data.....	70
	Drug Metabolism and In Vitro Drug-Drug Interactions.....	70
	In Vivo Drug-Drug Interaction Study.....	70
	Pharmacodynamics.....	71
	Exposure-Response.....	74
	Dose-Finding Rationale.....	75
	Immunogenicity.....	75
	General Biopharmaceutics.....	80
	Analytical Methods.....	83

### 3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

**Mechanism of Action:** ERBITUX (cetuximab) binds specifically to the epidermal growth factor receptor (EGFr, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of EGF and other ligands, such as transforming growth factor- $\alpha$ . Binding of cetuximab to the EGFr blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFr is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFr (HER1), HER2, HER3, and HER4. The EGFr is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFr is also detected in many human cancers including those of the colon and rectum.

*In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFr. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFr expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy agents alone.

**Single-Dose PK Parameters at Various Dose Levels:** The pharmacokinetics of cetuximab after single doses ranging from 5 to 500 mg/m<sup>2</sup> have been characterized in a broad range of studies and tumor types. Cetuximab exhibits nonlinear pharmacokinetics. AUC<sub>0- $\infty$</sub>  increased in a greater than dose proportional manner while an apparent linear relationship between cetuximab dose and mean C<sub>max</sub> was observed. Clearance (CL) decreased and half-life increased with increasing of doses. As the dose of cetuximab increased from 20 to 200 mg/m<sup>2</sup>, the clearance decreased from 0.08 to 0.02 L/h/m<sup>2</sup> and the half-life increased from 33 hours to 80 hours. At doses greater than 200 mg/m<sup>2</sup>, CL appeared to become constant. This plateau may be suggestive of a second, linear elimination pathway that becomes pronounced at doses above 200 mg/m<sup>2</sup>. The volume of distribution was observed to be independent of dose and consistent with a distribution of cetuximab in the vascular space of 2-3 L/m<sup>2</sup>.

**Multiple-Dose PK:** After administration of the target dose of 400 mg/m<sup>2</sup> initially and 250 mg/m<sup>2</sup> weekly, cetuximab peak and trough concentration were comparable across studies. Reasonably constant cetuximab peak and trough concentrations were generally reached within 3 to 5 weeks after the initiation of treatment and were maintained during later stages of the treatment without any accumulation.

**Drug Metabolism and In Vitro Drug-Drug Interaction:** No studies on the metabolism of cetuximab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety

Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids" and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P<sub>450</sub> enzyme system is not expected to play any role in cetuximab biotransformation.

***In Vivo Drug-Drug Interaction:*** A formal drug-drug interaction study of ERBITUX and irinotecan was performed and it did not reveal any evidence of a PK interaction between these two agents. In addition, the possible impact of radiation, cisplatin, paclitaxel, doxorubicin, gemcitabin, and irinotecan on the PK of cetuximab was evaluated in the population PK analysis. The results of this analysis indicated that these concomitant therapies did not have a demonstrable influence on the PK characteristics of cetuximab.

***Rationale for Dose Selection:*** In the early dose-escalation studies examining doses between 5 and 500 mg/m<sup>2</sup>, an acceptable safety profile was seen up to and including a 400 mg/m<sup>2</sup> weekly dose. Doses of 500 mg/m<sup>2</sup> produced an unacceptable high incidence of skin toxicity. A pharmacodynamic analysis of cetuximab on EGFr protein demonstrated maximal inhibition of EGFr expression across the 250-500 mg/m<sup>2</sup> dose range. At doses below 250 mg/m<sup>2</sup>, however, an increase in EGFr protein expression was observed, suggesting that therapeutic activity would be best maintained with dose at or above 250 mg/m<sup>2</sup>. An initial dose of 400 mg/m<sup>2</sup> followed by a weekly dose of 250 mg/m<sup>2</sup> was demonstrated to be well tolerated and efficacious across multiple studies. The pharmacokinetic behavior of cetuximab together with its pharmacodynamic activity on the EGFr is further supportive of both dose and regimen.

***Pharmacokinetics in Special Populations:*** No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted. A population PK analysis was conducted to investigate the potential effects of selected covariates including, hepatic and renal function, gender, race, weight, body surface area, and age on cetuximab pharmacokinetics. Female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on cetuximab pharmacokinetics.

***Inter-Individual Variability in PK Data:*** The integrated PK analysis investigated the inter-individual variability associated with the PK data. The population PK analysis identified gender as the only covariate, although this covariate did not require dose adjustment. The interpatient variability in the pharmacokinetic parameter estimates was low and ranged from 6 to 40%.

***Comparability among Product Lots:*** The ERBITUX lots administered in each of the studies was included in the dataset for population PK analysis. Different lots by different manufacturing processes appeared to not influence the resulting pharmacokinetics. But the product lots made in the BB36 manufacturing facility which were not included in this

analysis showed pharmacokinetically noncomparable to clinical lots manufactured in Lonza facility with 26% higher trough concentration and 52% higher peak concentrations.

**Pharmacodynamic Findings:** EGFr analysis in skin biopsies appeared to reveal a decrease in EGFr protein levels across the 250-500 mg/m<sup>2</sup> dose range, with a maximal effect reached at a dose of 400 mg/m<sup>2</sup>. An increase in EGFr protein levels appeared to occur at the 50 and 100 mg/m<sup>2</sup> doses. 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.

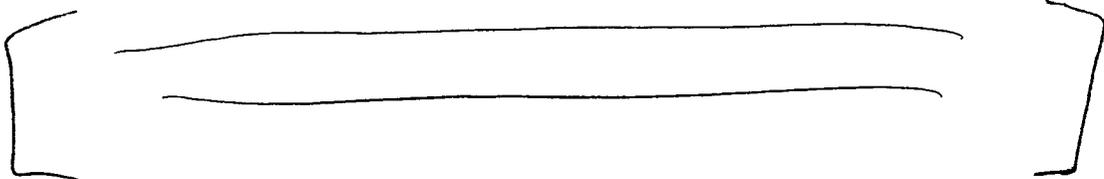
**Exposure-Response:** The potential relationship between cetuximab exposure and the EGFr status or the response as assessed by independent review and physician's assessment was explored in patients who had colorectal cancer and received the targeted ERBITUX dose. The derived intrinsic clearance from 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 it appeared to have no discernible relationship between skin rash and cetuximab systemic exposure.

**Immunogenicity:** As with all therapeutic proteins, cetuximab has the potential to induce an immune response. Due to limitations of assay performance, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. During the cetuximab clinical development program, patient sera were monitored for induction of an anti-cetuximab or human-chimeric antibody (HACA) response. Among patients who had both a negative pre-treatment sample and a post treatment sample available for analysis, non-neutralizing anti-cetuximab antibodies were detected in 5.3% (28/534) of evaluable patients with a median time to onset of 44 days (range 8-281 days). Although the number of sera-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity or PK of the molecule.

**Hypersensitivity:** In clinical trials, severe, potentially fatal hypersensitivity reactions have been reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In Studies in advanced colorectal cancer, severe hyperactivity reactions were observed in 2.5% of patients receiving ERBITUX plus irinotecan and 2.4% of patients receiving ERBITUX Monotherapy.

**Adverse Events:** The most common adverse events seen in patients receiving ERBITUX plus irinotecan were acne-like rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%). The most common grade 3 or 4 adverse events were diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acne-like rash (14%).

**Indication:**



**Dosage and Route of Administration:** The recommended dose of ERBITUX in combination with irinotecan or as monotherapy is 400 mg/m<sup>2</sup> 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<sup>2</sup> infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H<sub>1</sub> antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions.

2. *What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?*

None. Cetuximab-related changes in EGFr and p-EGFr in tumor biopsies showed inconsistent trends across dose and time making the results from these markers inconclusive. Cetuximab on p27 in tumor biopsies was variable and inconclusive. Ki67 expression appeared unaffected in both skin and tumor biopsies by single-dose cetuximab. Tumor expression of p-MAPK was variable and inconclusive. An attempt was made to measure EGFr saturation by immunohistochemistry. However, this method did not prove to be a suitable method due to analytical limitation.

Increasing exposure to cetuximab, as measured by AUC<sub>0-∞</sub>, corresponded to decreases in EGFr expression and increases in p-EGFr in skin biopsies. Maximum percent change in EGFr H-score occurred at AUC values greater than 10,000, corresponding to doses of at least 200 mg/m<sup>2</sup>.

**Table 2. PD Markers (Skin Biopsies)**

Drug exposure	PD marker	Effect	Time to maximum effect	Time to return to baseline
Single doses				
Doses ≥250 mg/m <sup>2</sup>	EGFr Protein Levels	↓, maximum ↓ at 400 mg/m <sup>2</sup>	Day 8	Day 15
<250 mg/m <sup>2</sup>		Slightly ↑		
Doses 50-500	p-EGFr expression	↑, maximum ↑ at 250 mg/m <sup>2</sup>	Day 2	
AUC <sub>0-∞</sub>	EGFr Protein Levels	↓, maximum ↓ at 10,000 µg.h/ml (doses of at least 200 mg/m <sup>2</sup> )		
	p-EGFr expression	Slightly ↑		
Doses 50-500	Cell cycle proteins p27, Ki67	Upregulation, independent of dose and exposure unaffected		
	MAPK	inadequate staining by immunohistochemistry		
	Expression of p-MAPK	Time-dependent down regulation	Days 8 and 15	Day 22
		No trend with regards to cetuximab dose or exposure		

## 4 Question-Based Review (QBR)

### 4.1 General Attributes

1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?*

**Chemistry and Physical-Chemical Properties:** ERBITUX (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor (EGFr) with affinity of 0.2 nM (Kd). ERBITUX is composed of the Fv regions of a murine anti-EGFr antibody with human IgG1 heavy and kappa light chain constant regions. Each heavy chain consists of \_\_\_\_\_ and each light chain consists of \_\_\_\_\_. It has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

**Formulation:** ERBITUX, is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible white amorphous cetuximab particulates.

**Table 1. ERBITUX Formulation**

Composition	Amount
Cetuximab	100 mg
Sodium phosphate dibasic heptahydrate	1.88 mg/ml
Sodium phosphate monobasic monohydrate	0.42 mg/ml
Sodium chloride	8.48 mg/ml
Water for Injection	qs 50 ml
pH	7.0-7.4

**Mechanism of Action:** Cetuximab binds specifically to the epidermal growth factor receptor (EGFr, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor- $\alpha$ . Binding of cetuximab to the EGFr blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFr is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFr (HER1), HER2, HER3, and HER4. The EGFr is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFr is also detected in many human cancers including those of the colon and rectum.

*In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFr. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFr expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy agents alone.

## 4.2 General Clinical Pharmacology

### 1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

**Response Endpoints:** In previous clinical trials of oncology agents, objective response has been shown to be a relevant and valid endpoint for evaluation of treatment effect for patients with metastatic colorectal cancer. In the clinical study of ERBITUX in colorectal cancer, objective response was defined as reduction in tumor burden measured by validated imaging procedures and was documented according to international standards. The use of the IRC (independent review committee) independent radiology assessment minimized the potential for the bias in interpretation of results. The objective response rates (ORR) in these populations are presented in Table 1 (FDA recommended labeling).

**Table 1: Objective Response Rates per Independent Review**

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI) <sup>a</sup>	p-value CMH <sup>b</sup>
	n	ORR (%)	n	ORR (%)		
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
•Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8, 25.6)	0.09
•Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

<sup>a</sup>95% Confidence interval for the difference in objective response rates. <sup>b</sup>Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

**Table 2: Time to Progression per Independent Review**

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI) <sup>a</sup>	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 - 0.71)	<0.001
•Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
•Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

<sup>a</sup>Hazard ratio of ERBITUX + irinotecan : ERBITUX monotherapy with 95% confidence interval.

**EGFr Expression and Response:** Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFr expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFr pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFr and

intensity (barely/faint, weak to moderate and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFr expression.

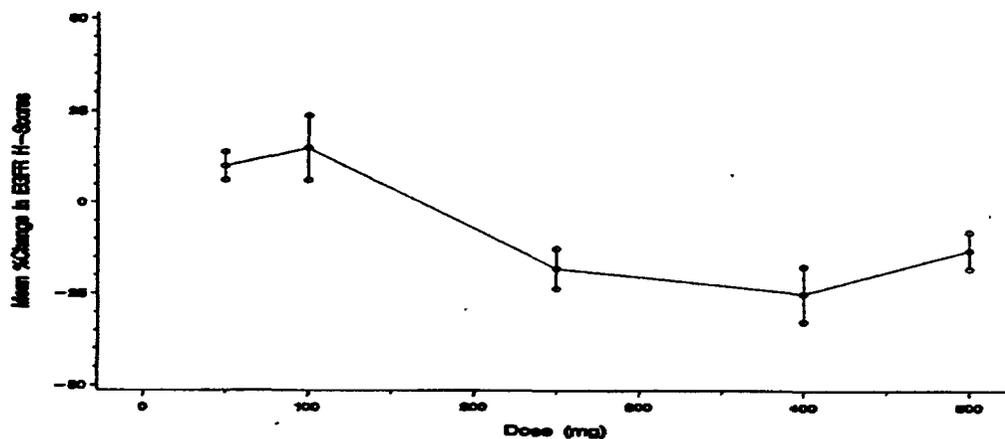
2. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to IV, F, Analytical Section; if no, describe the reasons)*

Cetuximab is a chimeric mouse/human monoclonal antibody of the IgG1 subclass that targets the human epidermal growth factor receptor (EGFr). As a competitive antagonist, cetuximab is being developed for the treatment of many EGFr-positive epithelial tumors. Three immunoassay methods (a Biacore assay (ImClone) and two ELISA (Merck KGaA and BMS)) have been used to determine the active moiety, cetuximab in serum. Within each study, only a single assay was used. To evaluate the comparability of these three bioanalytical methods and facilitate comparison of clinical results across different studies, a three-way cross-validation using incurred samples was performed (see Analytical Section). In addition, two assays were used for the determination of anti-cetuximab responses (see Analytical Section).

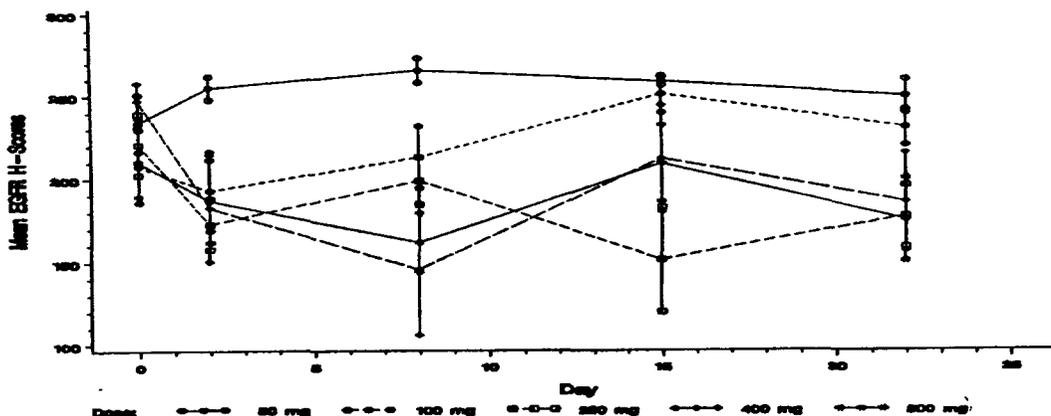
3. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?*

**Dose-Response:** In the early dose-escalation studies examining doses between 5 and 500 mg/m<sup>2</sup>, an acceptable safety profile was seen up to and including a 400 mg/m<sup>2</sup> weekly dose. Doses of 500 mg/m<sup>2</sup> produced an unacceptable high incidence of skin toxicity. A pharmacodynamic analysis of cetuximab on EGFr protein demonstrated maximal inhibition of EGFr expression across the 250-500 mg/m<sup>2</sup> dose range. At doses below 250 mg/m<sup>2</sup>, however, an increase in EGFr protein expression was observed, suggesting that therapeutic activity would be best maintained with dose at or above 250 mg/m<sup>2</sup>. An initial dose of 400 mg/m<sup>2</sup> followed by a weekly dose of 250 mg/m<sup>2</sup> was demonstrated to be well tolerated and efficacious across multiple studies.

Figure 1. Mean±SE Percentage Change in EGFr (Skin Biopsies) H-Score, Compared to Baseline, as a Function of ERBITUX Dose

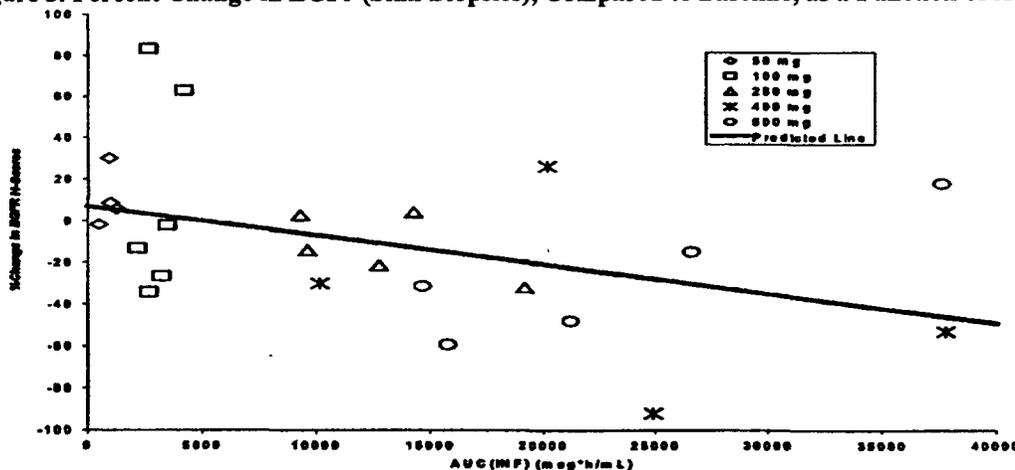


**Figure 2. Mean±SE Change in EGFr (Skin Biopsies) H-Score, Compared to Baseline, as a Function of ERBITUX Dose and Time**



**Exposure-Response:** The potential relationship between cetuximab exposure and the EGFr status or the response as assessed by independent review and physician's assessment was explored in patients who had colorectal cancer and received the targeted ERBITUX dose. Increasing exposure to cetuximab, as measured by  $AUC_{0-\infty}$ , corresponded to decreases in EGFr expression and increases in p-EGFr in skin biopsies. Maximum percent change in EGFr H-score occurred at AUC values greater than 10,000, corresponding to doses of at least 200 mg/m<sup>2</sup>. However, response rate did not correlate with either the percentage of positive cells or the intensity of EGFr expression.

**Figure 3. Percent Change in EGFr (Skin Biopsies), Compared to Baseline, as a Function of  $AUC_{0-\infty}$**



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 it appeared to have no discernible relationship between skin rash and cetuximab systemic exposure.

a) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration-time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m<sup>2</sup>. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m<sup>2</sup> as the dose increased from 20 to 200 mg/m<sup>2</sup>, and at doses >200 mg/m<sup>2</sup>, it appeared to plateau. The volume of the distribution (V<sub>d</sub>) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m<sup>2</sup>.

Figure 1. Plots of C<sub>max</sub>, AUC, CL and T<sub>1/2</sub> vs. Cetuximab Doses

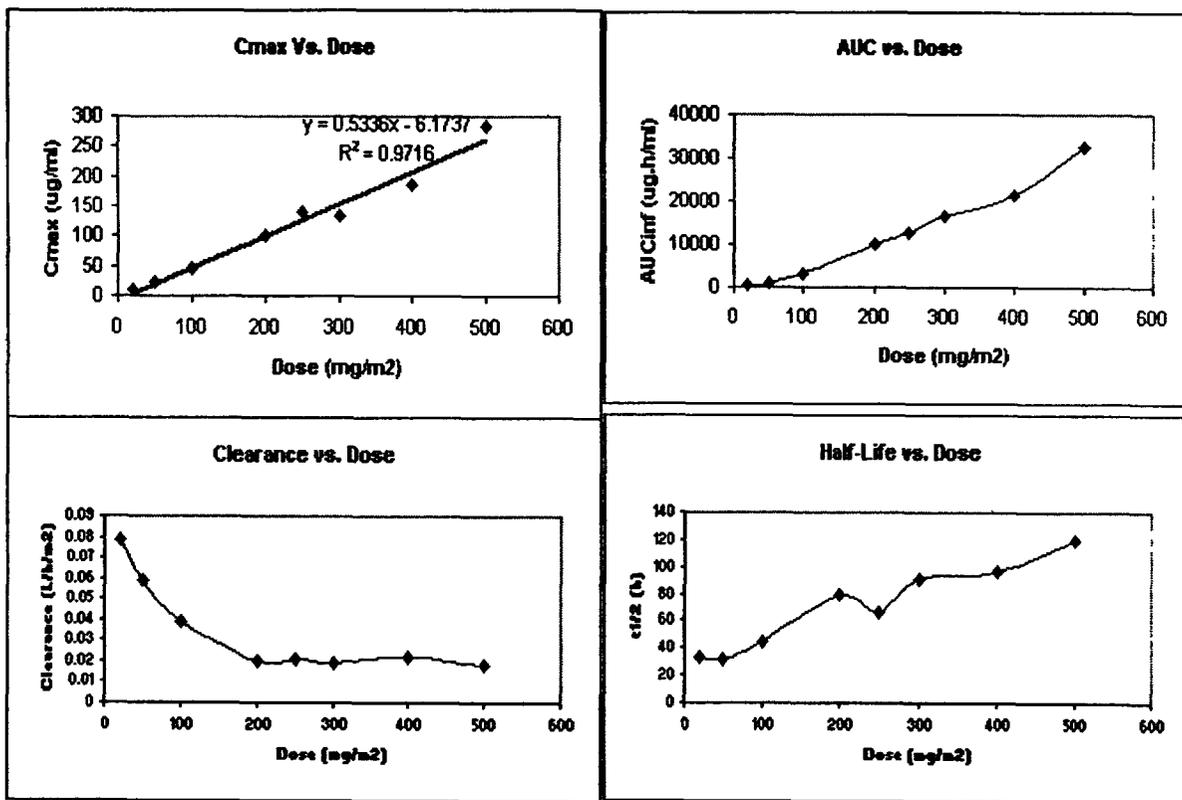
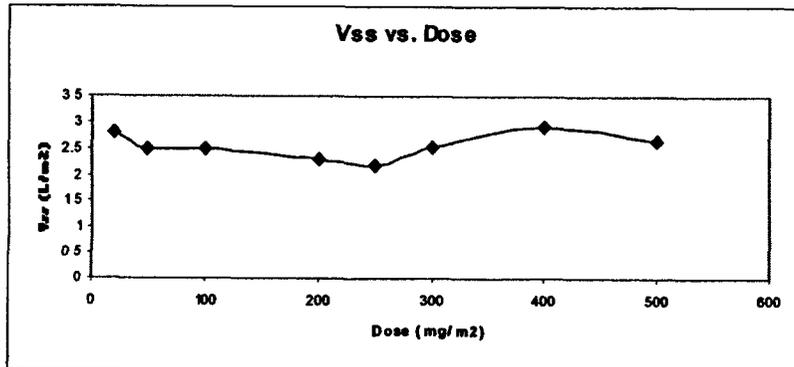


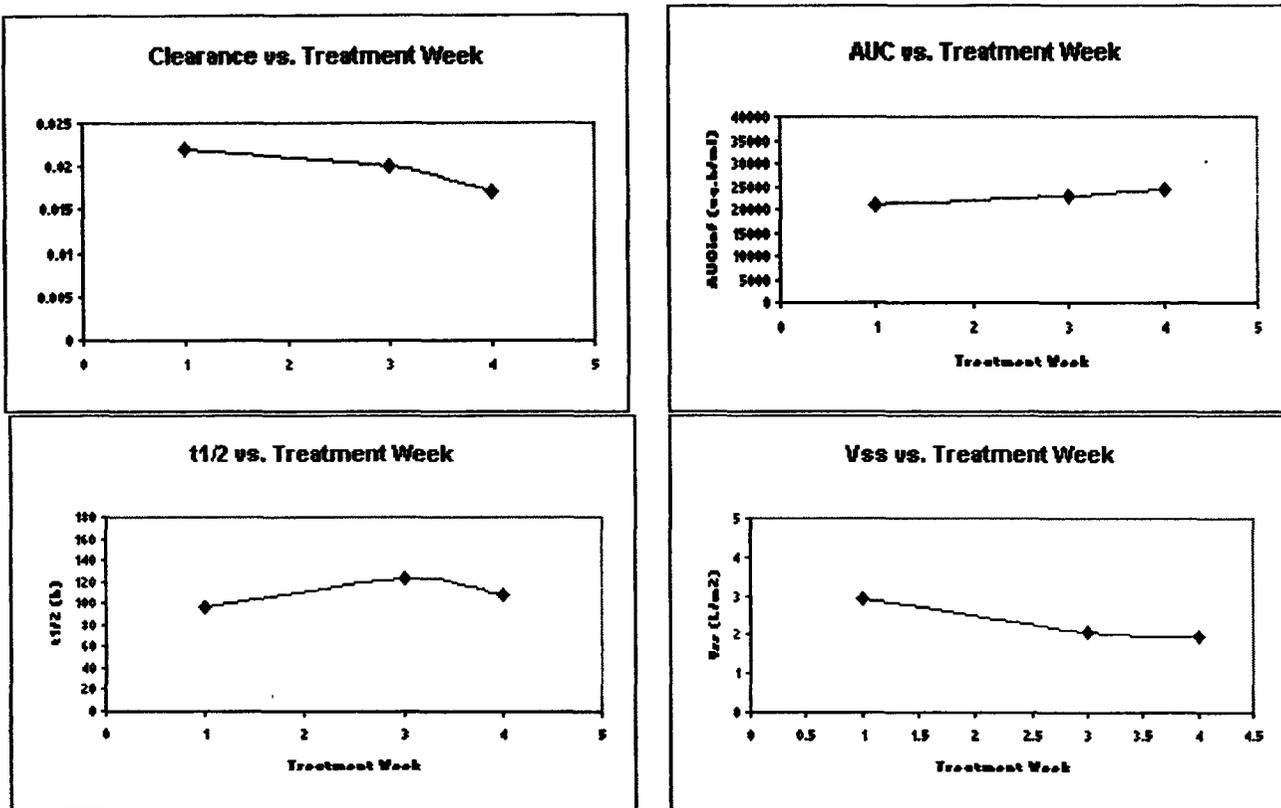
Figure 2. Plot of V<sub>ss</sub> vs. Cetuximab Doses



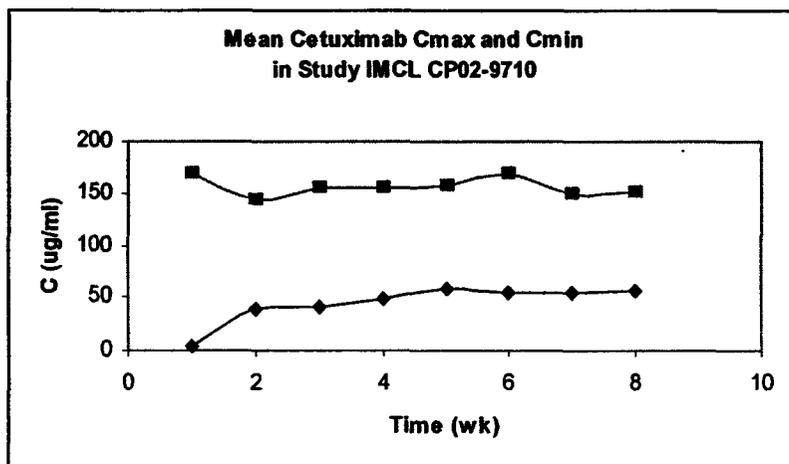
**b) Do PK parameters change with time following chronic dosing?**

No. PK parameters did not change with time following chronic dosing as demonstrated in the following plots.

**Figure 3. Plot of Treatment Week vs. Cetuximab PK Parameters**



**Figure 4. Plot of C<sub>max</sub> and C<sub>trough</sub> vs. Time**



**c) How long is the time to the onset and offset of the pharmacological response or clinical endpoint?**

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression.

**d) Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

There are no unresolved dosing or administration issues. In the early dose-escalation studies examining doses between 5 and 500 mg/m<sup>2</sup>, an acceptable safety profile was seen up to and including a 400 mg/m<sup>2</sup> weekly dose. Doses of 500 mg/m<sup>2</sup> produced an unacceptable high incidence of skin toxicity. A pharmacodynamic analysis of cetuximab on EGFr protein demonstrated maximal inhibition of EGFr expression across the 250-500 mg/m<sup>2</sup> dose range. At doses below 250 mg/m<sup>2</sup>, however, an increase in EGFr protein expression was observed, suggesting that therapeutic activity would be best maintained with dose at or above 250 mg/m<sup>2</sup>. An initial dose of 400 mg/m<sup>2</sup> followed by a weekly dose of 250 mg/m<sup>2</sup> was demonstrated to be well tolerated and efficacious across multiple studies. The pharmacokinetic behavior of cetuximab together with its pharmacodynamic activity on the EGFr is further supportive of both dose and regimen.

**4. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

The pharmacokinetic information for intravenously administered ERBITUX submitted in this application was obtained from 906 cancer patients in a total of 19 studies. No studies were conducted in healthy volunteers.

**a) What are the basic PK parameters?**

**Table 1. Single-Dose PK Parameters for Cetuximab Cross all Studies (mean±SD)**

Dose (mg/m <sup>2</sup> )	N	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )
20	13	8.7±4.2	343±228	33.3±29.2	0.079±0.039	2.81±1.09
50	23	22.2±4.7	1031±440	32.3±9.8	0.059±0.028	2.49±0.70
100	52	46.8±11.6	2912±1060	44.8±12.8	0.039±0.015	2.48±0.91
200	14	102.4±29.4	9923±3226	79.8±19.6	0.020±0.010	2.31±1.05
250	8	140.2±19.6	12414±3332	65.9±18.8	0.021±0.005	2.17±0.16
300	4	133.2±47.7	16311±3786	90.4±13.8	0.019±0.005	2.52±0.49
400	56	184.5±54.6	21142±8657	97.2±37.4	0.022±0.009	2.91±0.90
500	20	283.8±84.1	32448±12880	119.4±76.9	0.018±0.008	2.63±0.66

**Table 2. PK Parameters in Multiple Dose Studies at the Target Dose (400 mg/m<sup>2</sup> initial [week 1], 250 mg/m<sup>2</sup> weekly) (mean±SD)**

Parameter	CL (L/h/m <sup>2</sup> )	AUC (µg.h/ml)	t <sub>1/2</sub> (h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Week 1 (N=53)	0.022±0.009	21143±8657	97.2±37.4	2.91±0.90
Week 3 (N=8)	0.020±0.006	22723±10313	123.2±41.4	2.08±0.52
Week 4 (N=13)	0.017±0.006	24329±11202	108.1±29.3	1.99±0.59

Following a 2-hour infusion of 400 mg/m<sup>2</sup> of ERBITUX, the maximum mean serum concentration (C<sub>max</sub>) was 184 µg/mL (range: \_\_\_\_\_) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m<sup>2</sup> produced a mean C<sub>max</sub> of 140 µg/mL (range \_\_\_\_\_). Following the recommended dose regimen (400 mg/m<sup>2</sup> initial dose / 250 mg/m<sup>2</sup> weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

**b) Is this a high extraction ratio or a low extraction ratio drug?**

Not applicable.

**c) Does mass balance study suggest renal or hepatic the major route of elimination?**

No mass balance study has been conducted for cetuximab. Cetuximab is a monoclonal antibody. Mass balance studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that then recycled into other proteins.

**5. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

The integrated PK analysis investigated the inter-individual variability associated with the PK data. The population PK analysis identified gender as the only covariate, although this statistical significance in PK did not require dose adjustment. The interpatient variability in the PK parameter estimates was low and ranged from 6 to 40%.

#### **4.3 Intrinsic Factors**

**1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

**Pharmacokinetics in Special Populations:** No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted. A population PK analysis was conducted to investigate the potential effects of selected covariates including, hepatic and renal function, gender, race, weight, body surface area,

and age on cetuximab pharmacokinetics. Female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on cetuximab pharmacokinetics

**2. Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

**a) Elderly**

Of the 633 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 206 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients. Age was used as a covariate in population PK analysis and it appeared to not have an impact on cetuximab pharmacokinetics.

**b) Pediatric Patients**

The safety and effectiveness of ERBITUX in pediatric patients has not been established.

**c) Gender**

Female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary.

**d) Race**

In the population PK database, 821 patients were Caucasians; 45 patients were Blacks; 18 patients were Asians; 14 were Hispanics and 8 patients were others. Race was used as a covariate in population PK analysis and it appeared to not have an impact on cetuximab pharmacokinetics.

**e) Renal Impairment**

In the population PK database, there were 564 patients with normal renal function, 289 patients with mildly, 49 patients with moderately, and 4 patients with severely impaired renal function. Renal function was used as a covariate in population PK analysis and it appeared to not have an impact on cetuximab pharmacokinetics.

**f) Hepatic Impairment**

In the population PK database, there were 835 patients with normal hepatic function, 23 patients with mildly, 24 patients with moderately, and 14 patients with severely impaired hepatic function. Hepatic function was used as a covariate in population PK analysis and it appeared to not have an impact on cetuximab pharmacokinetics.

**g) What pregnancy and lactation use information is there in the application?**

***Pregnancy Category C:*** 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 cetuximab has the potential to be transmitted from the mother to the developing fetus. It is not known whether cetuximab can cause fetal harm when administered to a pregnant woman or whether cetuximab can affect reproductive capacity. There are no adequate and well-controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

***Nursing Mothers:*** It is not known whether cetuximab is secreted in human milk. Since human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. Based on the mean half-life of cetuximab after multiple dosing of 114 hours [range 75-188 hours], women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

***h) Other factors that are important to understanding the drug's efficacy and safety***

***Immunogenicity:*** As with all therapeutic proteins, cetuximab has the potential to induce an immune response. Due to limitations of assay performance, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. During the cetuximab clinical development program, patient sera were monitored for induction of an anti-cetuximab or human-chimeric antibody (HACA) response. Among patients who had both a negative pre-treatment sample and a post treatment sample available for analysis, non-neutralizing anti-cetuximab antibodies were detected in 5.3% (28/534) of evaluable patients with a median time to onset of 44 days (range 8-281 days). Although the number of sera-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity or PK of the molecule.

***Hypersensitivity:*** In clinical trials, severe, potentially fatal hypersensitivity reactions have been reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In Studies in advanced colorectal cancer, severe hyperactivity reactions were observed in 2.5% of patients receiving ERBITUX plus irinotecan and 2.4% of patients receiving ERBITUX Monotherapy.

***Infusion Reactions:*** If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (FDA recommended labeling)

**Dermatologic Toxicity and Related Disorders:** If a patient experiences severe acneform rash, ERBITUX treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (FDA recommended labeling)

**ERBITUX Dose Modification Guidelines**

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m <sup>2</sup> Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200 mg/m <sup>2</sup> Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150 mg/m <sup>2</sup> Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

#### 4.4 Extrinsic Factors

1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?*

Except concomitant drug administration, other factors have not been studied.

2. *Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.*

None.

#### 3. Drug-Drug interactions

a) *Is there an in vitro basis to suspect in vivo drug-drug interaction?*

No.

b) *Is the drug a substrate of CYP enzymes?*

No.

c) *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

No.

d) *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

No.

**e) Are there other metabolic/transporter pathways that may be important?**

No studies on the metabolism of cetuximab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, “the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids” and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P<sub>450</sub> enzyme system is not expected to play any role in cetuximab biotransformation.

**f) Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?**

A formal drug-drug interaction study of cetuximab and irinotecan was performed and it did not reveal any evidence of a PK interaction between these two agents.

**Table 1. Study Design**

	Irinotecan Single dose 350 mg/m <sup>2</sup>	Cetuximab 400 mg/m <sup>2</sup>	250 mg/m <sup>2</sup>	PK Data
Group A (n=6)	Weeks 1 and 4	Week 2	Weeks 3 and 4	Irinotecan PK
Group B (n=8)	Week 4	Week 1	Weeks 2, 3, and 4	Cetuximab PK

**Table 2. PK Parameters of Cetuximab in Group B (N=7, M/F 3/4) (mean±SD)(median)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-4</sub> (µg.h/ml)	t <sub>1/2</sub> (h)
WK 3 (alone)	153±38 (138)	13039±4783 (12874)	119±42 (100)
WK 4 (combo)	162±43 (168)	14923±5029 (16183)	117±32 (106)
WK 4/WK 3	106±11% (104%)	117±14% (108%)	107±38% (103%)
Parameter	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )	
WK 3 (alone)	0.020±0.006 (0.019)	2.07±0.55 (1.95)	
WK 4 (combo)	0.018±0.007 (0.015)	1.89±0.55 (1.89)	
WK 4/WK 3	91±8% (92%)	92±13% (93%)	

**Table 3. PK parameters of Irinotecan in Group A (N=6, M/F 3/3) (mean±SD)(median)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-4</sub> (µg.h/ml)	AUC <sub>0-∞</sub> (µg.h/ml)
WK 1 (alone)	8129±2882 (7071)	42792±22277 (33064)	44243±23683 (33857)
WK 4 (combo)	6783±1293 (6474)	39051±16852 (37598)	40394±18365 (38251)
WK 4/WK 1	90±29% (87%)	96±22% (97%)	96±21% (98%)
Parameter	t <sub>1/2</sub> (h)	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )
WK 1 (alone)	9.8±2.6 (9.9)	9.7±4.2 (10.4)	83±21 (82)
WK 4 (combo)	9.8±2.0 (9.4)	10.0±4.3 (9.2)	85±15 (84)
WK 4/WK 1	102±16% (102%)	107±26% (99%)	106±21% (109%)

**g) What other co-medications are likely to be administered to the target patient population?**

The possible impact of radiation, cisplatin, paclitaxel, doxorubicin, gemcitabin, and irinotecan on the PK of cetuximab was evaluated in the population PK analysis. This analysis indicated that these concomitant therapies did not have a demonstrable influence on the PK characteristics of cetuximab.

**h) Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

None.

**i) Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

None.

**j) Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

None.

#### 4.5 General Biopharmaceutics

**1. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?**

The efficacy results from three clinical trials (EMR 62 202-007, IMCL-9923 and IMCL-0141) form the basis to support an accelerated approval of ERBITUX for the proposed indication. The to-be-marketed product manufactured in Lonza facility was used in these clinical trials.

The sponsor originally proposed to market the product manufactured in BB36 facility which was only used in the ongoing clinical trial IMCL-0144.

**Table 1. Product Lots Used in Clinical Trials**

Trial Number	Product Lot Number	Manufacturing Sites
IMCL CP02-9923	980452, 990261, 990609, 990388, 990764, 990819, 000007, 00C00453, 01C00006, 01C00090, 00C00660, 00C00664, 01C00503	Lonza
IMCL CP02-0141	00C01178, 00C00010	Lonza
EMR 62 202-007	00C001178, 01C01178, 00C01178, 00C00453, 00C00006, 00C00010, 00C0090	Lonza
IMCL CP02-0144 (ongoing)	02C00001B	BB36

Cetuximab concentration data were available from 25 patients in the ongoing trial CP02-0144. Comparisons of peak and trough concentrations between BB36 and Lonza manufacturing sites are shown in the following table:

**Table 2. Comparison of Peak and Trough Concentrations between BB36 and Lonza Facilities (mean±SD)**

Manufacturing Site	Lonza	BB36	GM Ratio	P
C <sub>peak</sub> (µg/ml)	205±74	312±110	1.52	0.0016
C <sub>trough</sub> (µg/ml)	60±30	112±64	1.26	>0.05

The geometric mean ratio between BB36 and Lonza associated pharmacokinetic values were 1.26 for the trough and 1.52 for the peak, and both failed to meet criteria for comparability.

**a) What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

Trial 0144 was planned to enroll 250 patients. In the present submission, efficacy and safety data from 111 patients were reported and among them 25 patients had cetuximab peak and trough concentrations available. Although peak and trough concentrations were higher in Trial 0144 compared to other trials, the initial data showed the percentage of patients with severe skin rash similar among trials.

**Table 3. Severe Skin Rash Incidence by Trial**

Study Number	62 202-007	CP 02-9923	02-0141	02-0144	02-9710
#Patient treated	329	138	57	111	54
#Severe skin rash	47	20	7	10	7
Percentage	14.3%	14.4%	12.3%	9%	13%

**b) If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?**

Clinical and pharmacokinetic data support the approval of the product manufactured at Lonza facility. Since product manufactured at BB36 facility is not pharmacokinetically comparable to the clinical trial product manufactured at Lonza facility, the sponsor is requested to submit the complete efficacy and safety results of Trial CP02-0144 as a supplement to support the marketing of the product manufactured at BB36 facility.

**c) If the formulations are not BE, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation? (e.g., dosage adjustments may be made for injectables)**

Not applicable.

2. *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

Not applicable because ERBITUX is given via intravenous infusion.

3. *When would a fed BE study be appropriate and was one conducted?*

Not applicable.

4. *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

Not allocable.

#### 4.6 Analytical

1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Three immunoassay methods (a Biacore assay (ImClone) and two ELISA (Merck KGaA and BMS)) have been used to determine the active moiety, cetuximab in serum.

2. *Which metabolites have been selected for analysis and why?*

None.

3. *For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?*

Not applicable because cetuximab is a protein.

4. *What bioanalytical methods are used to assess concentrations?*

**Cetuximab Assay:** Three immunoassay methods (a Biacore assay (ImClone) and two ELISA (Merck KGaA and BMS)) have been used to determine the active moiety, cetuximab in serum. Within each study, only a single assay was used.

**Table 1. Assays Used in Clinical Trials**

Assay Method	Clinical Trials
Biacore (ImClone):	IMCL CP02-9923, IMCL CP02-0141, IMCL CP02-9710, IMCL CP02-0144
ELISA (Merck KGaA):	EMR 62 202-007, EMR 62 202-012

**Table 2. Curve Fitting Equations and Range of Standard Curves**

Method	Curve Fitting Equation	Range of Standard Curve
BMS,	$Y = \max + \frac{(\min - \max)}{1 + (\text{conc}/\text{ED50})^b}$	_____
Merck KGaA	$y = a - d/[1 + (x/c)^b] + d$	_____
Biacore	$y = a - d/[1 + (x/c)^b] + d$	_____

To ensure that measured concentrations fall within the limited standard curve range, each individual sample assayed at BMS was assayed at different dilutions. If two of the dilution samples fell within the standard curve range, the value reported was that which was closest to the mid-point of the curve.

At Merck KGaA, to ensure that measured concentrations fall within the limited standard curve range, each individual sample assayed at Merck KGaA was assayed at \_\_\_\_\_ of those dilutions were selected which fitted best in the linear range of the standard curve. From these \_\_\_\_\_ dilutions, the value which was closest to the inflection point of the curve was reported.

At ImClone, this equation was used to describe the relationship between the \_\_\_\_\_ response units and nominal concentrations of cetuximab standards in each run. Clinical serum samples need to be diluted in assay buffer at a minimum dilution of \_\_\_\_\_ to reduce interference by human serum components. Cetuximab concentrations in nM were converted to µg/ml by multiplying by a factor of 0.1512 (MW=152,100 Dalton).

The correlation coefficient values ( $r^2$ ) for the standard curves from all runs were >0.997. In each plate, the deviations of the back-calculated concentrations from their nominal values were within ±15% (±20% from LLOQ) for at least three-fourths of the calibration standards.

**Assay Comparability:** To evaluate the comparability of these three bioanalytical methods and facilitate comparison of clinical results across different studies, a three-way cross-validation using incurred samples was performed (Table 3). Comparability of the three assays was demonstrated as shown in Table 4.

**Table 3. Evaluation of Assay Performance**

Method	Intra-assay Precision (%CV)	Inter-assay Precision (%CV)	Accuracy (of the nominal value)	Concentration Range (µg/ml)
BMS	9.5%	2.0%	94-106%	_____
Merck KGaA	15%	7.5%	98-105%	_____
Biacore	15%	15%	85-115%	_____

**Table 4. Comparison of the Accuracy and Precision of Three Immunoassays**

	Mean Concentration (µg/ml) with Pooled SD		
	BMS	ImClone	Merck KGaA
Overall	140.6 (14.0)	173.2 (24.6)	148.7 (13.4)
% Deviation from grand mean (154.1) with RSD (%)	-8.8% (10.0)	12.3% (14.2)	-3.5% (9.0)

The three assays for the determination of cetuximab in human serum have been validated to be sufficiently accurate, precise, linear and rugged for their intended purpose.

**Anti-Cetuximab Response Assay:** Two assays were used for the determination of anti-cetuximab responses. The assay used by ImClone to determine anti-cetuximab reactivity was a non-species-specific, double-antigen, radiometric assay specific for cetuximab. In the Merck studies a sandwich ELISA was used to determine the anti-cetuximab

responses. Both the ImClone and Merck assays are based on a similar principle that relies on capture and detection of anti-cetuximab antibodies by cetuximab itself.

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34 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

## 6.2 Individual Study Reviews

### Product Development Rationale

Colorectal cancer causes much morbidity and mortality in our society. There are over 150,000 new cases per year in the US, with over 1,000,000 new diagnoses each year worldwide. One third to one half of this number dies each year from colorectal cancer primarily from metastatic disease. Even with the best currently available therapies, median survival for patients with metastatic colorectal cancer is 20 months and more than 90% will die within 5 years.

Currently available therapies for metastatic colorectal cancer have made incremental advances over supportive care. Various regimens containing 5-fluorouracil (5-FU) and leucovorin were the standard for over 30 years. Recently two additional cytotoxic chemotherapeutic agents have become available. Irinotecan was first approved to treat colorectal cancer in the mid 1990s and became a key component in regimens that defined the standard of care for first- or 2<sup>nd</sup>-line therapy for metastatic disease. Oxaliplatin was approved in second-line therapy after failure of irinotecan, but is also showing promising results in the first-line setting. Unfortunately, almost all patients eventually develop progressive disease despite treatment. Once a patient progresses while on chemotherapy, there is little, if any, effective therapy available. For example, patients who progressed during or within 6 months of irinotecan/5-FU/leucovorin therapy have only a 1% response rate to oxaliplatin and a 9% response rate to a combination of oxaliplatin/5-FU/leucovorin. Time to progression is improved with the combination; however, once a patient has failed these agents there are no effective therapeutic options. The clinical development of cetuximab has targeted patients who failed 5-FU and irinotecan; many have also failed oxaliplatin.

### Clinical Pharmacology and Pharmacokinetics Program

**Overall Assessment of Clinical Pharmacology:** The PK profile of cetuximab has been comprehensively characterized in a variety of studies and tumor types. The pharmacokinetics of cetuximab is predictable. Furthermore, cetuximab was not found to interact with irinotecan as shown in a formal drug-drug interaction study. The incidence of HACA is low and does not appear to impact clinical outcome. In summary, based on all available safety, efficacy, PK/PD and immunogenicity data, the chosen dosing of an initial cetuximab dose of 400 mg/m<sup>2</sup> followed by a weekly dose of 250 mg/m<sup>2</sup> is safe and effective.

**Data:** The PK information contained in this application is based on serum cetuximab concentration data obtained from a total of 906 patients in various tumor types including prostate cancer, breast cancer, SCCHN, renal cancer, CRC, melanoma, and NSCLC. No studies in healthy subjects were performed with cetuximab.

**Data Source**

	#Trials	#Subjects	Trial #
Dose-escalation Studies (5-500 mg/m <sup>2</sup> )	10	175	IMCL: CP02-9401, 9502, 9503, 9504, 9605, 9607, 9608, 9709 BMS: CA225004, CA225005
Target Dose Studies (400 mg/m <sup>2</sup> followed by weekly doses of 250 mg/m <sup>2</sup> )	9	731	IMCL: CP02-9710, 9813, 9814, 9816, 9923, 0038, 0141, EMR: 62, 202-007, 012

**Assay:** In the clinical development program, serum cetuximab concentrations were measured using different assays: validated enzyme-linked immunosorbent assay (ELISA) methods (Merck and BMS studies, reported in µg/ml) and a validated Biacore-<sub>1</sub> assay (ImClone studies, reported as nmo/L). In the Clinical Summary, all units are presented in micrograms per milliliter. A molecular weight of 152.1 kD was used for the conversion of the units. Results from cross validation tests of these assays demonstrated that the 3 assays were comparable.

**Pharmacokinetics*****Dose-Escalation Studies (Single Dose)***

There were ten open-label dose-escalation studies in which cetuximab was administered as an intravenous infusion. Study IMCL CP02-9401 was a single-dose trial; the 9 remaining studies were multiple-dose studies. Typically, non-compartmental pharmacokinetic analyses were performed on the initial infusion of treatment. Across all dose escalation studies the observed trends in cetuximab pharmacokinetics were consistent. The V<sub>ss</sub> was small (approx. 2-3 L/m<sup>2</sup>) and approximated the volume of the vascular space. Increases in cetuximab AUC<sub>0-∞</sub> appeared to be greater than dose proportional because CL (L/hr/m<sup>2</sup>) decreased with increasing dose. T<sub>1/2</sub> increased with increasing dose. These observations suggest that cetuximab pharmacokinetics are non-linear. Cetuximab trough and peak concentrations reached constant levels from the third infusion onward. Pharmacokinetic data obtained from dose-escalation studies (single dose) are summarized in the following tables.

**Table 1. IMCL CP02-9401 (Mean±SD) (Process/Batch #, = 423704, 500301)**

Parameter Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
5 (n=3)	0.3±0.6	ND	ND	ND	ND
20 (n=3)	7.7±2.1	194±23	15.3±0.7	0.10±0.01	2.35±0.43
50 (n=3)	23.0±3.5	1058±142	32.5±5.1	0.04±0.01	2.30±0.65
100 (n=4)	51.0±10.0	2566±597	42.3±11.7	0.04±0.01	2.34±0.32

Blood sampling for cetuximab concentration measurement were at 0, 1, 3, 6, 24, 48, 72, 96 h, days 8, 15, and 28 after the first dose.

**IMCL CP02-9401 Summary:** Increase in cetuximab AUC<sub>0-∞</sub> appeared to be greater than dose proportional, whereas CL values decreased with dose. The volume of distribution appeared to be constant and independent of dose.

**Table 2. IMCL CP02-9502 (Mean±SD) (Process/Batch #, — : 423704, 500301)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
5 (n=3)	3.3±4.9	ND	ND	ND	ND
20 (n=4)	13.0±4.3	334±171	23.0±9.2	0.07±0.03	2.09±0.30
50 (n=3)	25.3±3.5	1217±534	33.8±8.6	0.05±0.02	2.10±0.39
100 (n=7)	58.3±10.2	3135±785	42.2±4.3	0.03±0.01	2.14±0.57

Blood sampling for cetuximab concentration measurement were at 0, 5 min, 1, 3, 6, 96, 168h after 1<sup>st</sup>, 2<sup>nd</sup>, and 4<sup>th</sup> doses.

**IMCL CP02-9502 Summary:** At the 20, 50, and 100 mg/m<sup>2</sup> doses, the increase in values for AUC appeared to be greater than dose proportional. There appeared to be a trend to a decrease in CL and an increase in t<sub>1/2</sub> with increasing dose. The volume of distribution V<sub>ss</sub> remained constant. The same product batches were used, but AUC values were higher in this study compared to those in IMCL CP02-9401.

**Table 3. IMCL CP02-9503 (Mean±SD) (Process/Batch #, — 423704, 500301, 950012, 960159, and 960223)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
5 (n=5)	1.6±0.9	ND	ND	ND	ND
20 (n=3)	8.7±0.6	524±310	62.4±43.0	0.05±0.03	3.32±0.93
50 (n=1)	16.0	598	22.7	0.08	2.79
100 (n=3)	38.3±14.6	2343±1118	36.9±12.6	0.05±0.02	3.06±2.00
200 (n=3)	89.0±11.4	8557±988	81.5±13.4	0.015±0.013	1.76±1.54
400 (n=2)	189.0±31.1	19028	84.2	0.021	2.52

(All groups Cisplatin 60 mg/m<sup>2</sup> monthly). Blood sampling for cetuximab concentration measurement were at multiple time points after dose 1 and 3 (1, 24, 48, and 96h post-infusion), trough levels later.

**IMCL CP02-9503 Summary:** At doses greater than 5 mg/m<sup>2</sup>, the increase in value for AUC appeared to be greater than dose proportional. There appeared to be a trend towards a decreased in CL and an increase in t<sub>1/2</sub> with increasing doses of cetuximab. Cetuximab PK parameters were in agreement with those seen at the same dose levels in the previous studies.

**Table 4. IMCL CP02-9504 (Mean±SD) (Process/Batch #, — 950012, 960159, 960223, 960275, 960430, 970002, and 970311)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
20 (n=3)	4.0±1.0	133	23.1	0.15	5.09
50 (n=4, D-15)	24.3±2.1	1641±482	46.0±11.7	0.033±0.012	2.10±0.30
50 (n=4, D-20)	20.5±0.7	1050±66	38.2±5.9	0.048±0.003	3.27±1.48
100 (n=8, D-15)	45.8±14.4	3097±1146	46.2±10.1	0.036±0.016	2.33±0.69
100 (n=8, D-20)	44.4±9.1	2976±633	50.7±10.4	0.035±0.006	2.55±0.54
200 (n=3)	123.9±22.8	12012±2992	87.3±23.1	0.018±0.004	2.08±0.29
400*/200 (n=4)	128.5±19.1	17705±2010	107.2±18.7	0.023±0.003	3.53±0.97
300 (n=3)	133.2±47.7	16311±3786	90.4±13.8	0.019±0.005	2.52±0.49

(All groups were on Doxorubicin 15 or 20 mg/m<sup>2</sup> D-15 or D-20) (\*initial dose). Blood sampling for cetuximab concentration measurement were at 0, 5 min, 1, 1.25, 24, 48, 72, 96, 120, 144, and 168h after 1<sup>st</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 6<sup>th</sup> doses.

**IMCL CP02-9504 Summary:** The increase in values for AUC appeared to be greater than dose proportional. There appeared to be a trend towards a decrease in CL and an increase in  $t_{1/2}$  with increasing dose. At dose levels of 200 mg/m<sup>2</sup> and higher, values for CL and  $t_{1/2}$  appeared to be relatively constant.

**Table 5. IMCL CP02-9605 (Mean±SD) (Lot #: 950012, 960159, 960223, 960275, and 970002)**

Parameter Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
50 (n=3, P-175)	16.0	766	40.7	0.065	3.24
100 (n=6, P-175)	38.7±15.6	2562±1265	48.4±8.1	0.047±0.022	3.38±1.64
100 (n=3, P-80)	54.3±8.5	4779±2422	63.5±28.3	0.024±0.011	1.96±0.08

(Groups 1 and 2 were on Paclitaxel 175 mg/m<sup>2</sup> once every three weeks P-175 and Group 3 was on 80 mg/m<sup>2</sup>). Blood sampling for cetuximab concentration measurement were at 0, 1, 1, 24, 48, 144h on doses 1, 3, and 5 and trough levels + 1 h post dose for other doses.

**IMCL CP02-9505 Summary:** The sponsor concluded that C<sub>max</sub> and AUC values for cetuximab did not differ after co-administration of 2 dose levels of paclitaxel.

**Table 6. IMCL CP02-9607 (Mean±SD) (Process/Batch #, — 960275, 960430, 970002, 970311, PS2 980077)**

Parameter Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
100/100 (n=3)	46.0±5.7	2526±41	32.7±7.6	0.040±0.001	2.21±0.03
200/200 (n=3)	82.0±13.9	8162±1836	62.8±8.6	0.025±0.005	2.46±0.28
400/2000 (n=3)	280	40526±7520	177.2±51.2	0.010±0.002	2.46±0.26
500/250 (n=2)	317.5±115.3	41308±1804	106.7±12.9	0.012±0.001	1.88±0.32
400/250 (n=3)	196.5±61.5	21337±5541	81.9±12.2	0.019±0.005	2.41±1.02

Radiation (weeks 2-8): Once daily in groups 1-4 with total dose 70 Gy, twice daily in group 5 with total dose 76.8 Gy. Blood sampling for cetuximab concentration measurement were at 1, 24, 48, 72, and 96 h after doses 1, 4, 8, and 9; trough levels + 1 h post dose for other doses.

**IMCL CP02-9505 Summary:** The increase in values for cetuximab AUC was greater than dose proportional. There appeared to be a trend towards a decrease in CL and an increase in  $t_{1/2}$  with increasing dose.

**Table 7. IMCL CP02-9608 (Mean±SD) (Process/Batch #, — 960275, 960430, 970002, PS2 980253)**

Parameter Dose (mg/m <sup>2</sup> )	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
100/100 (n=3)	41.0±5.4	2774±995	39.4±3.0	0.040±0.0171	2.36±0.96
500/250 (n=3)	311	27076	68.4	0.018	1.85
400/2500 (n=5)	208.5±37.5	32.28±22643	133.3±93.5	0.017±0.012	2.47±0.08

Cisplatin: 100 mg/m<sup>2</sup> once every 3 weeks. Blood sampling for cetuximab concentration measurement were at 1, 24, 48, and 96 h after doses 1, 4, 5 and then trough levels.

**IMCL CP02-9608 Summary:** The increases for cetuximab AUC were greater than dose proportional. There appeared to be a trend towards a decrease in CL and an increase in  $t_{1/2}$  with dose. Values for V<sub>ss</sub> remained constant over the dose range tested.

**Table 8. IMCL CP02-9709 (Mean±SD) (Process/Batch # — : 960223, 960275, 970002, PS2 980253)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Dose (mg/m <sup>2</sup> )					
400/250 (n=1)	53.0	4682	73.7	0.042	5.05
200/200 (n=1)	192.0	22128	113.4	0.018	2.94

Blood sampling for cetuximab concentration measurement were at 1, 24, 48, 72, and 96 h after doses 1, and 3; trough levels + 1 h post dose for the 2<sup>nd</sup> dose. In addition, daily samples after the 96 h post-infusion sample for one week following the 3<sup>rd</sup> and final infusion.

**IMCL CP02-9709 Summary:** Due to small number of patients no PK conclusions were reached.

**Table 9. BMS CA225004 (Mean±SD) (Process/Batch # — 01C00010, 02C00063)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Dose (mg/m <sup>2</sup> )					
50 (n=5)	21.2±8.3	783±461	25.4±7.8	0.083±0.410	2.69±0.86
100 (n=5)	49.1±13.1	2366±882	38.7±14.7	0.049±0.023	2.54±1.12
250 (n=3)	124.9±4.5	11409±2000	56.4±9.5	0.022±0.004	1.82±0.44
400 (n=6)	229.4±52.9	21258±6826	78.0±16.5	0.020±0.005	2.22±0.58
500 (n=5)	291.6±89.1	40997±14136	178.5±96.8	0.013±0.004	3.03±0.68

Blood sampling for cetuximab concentration measurement were at pro-dose, 1, 1.58, 2.5, 3, 4, 6, 8, 24, 48, 96, 168, 264, 336, 432, and 504 h (Day 22) after the start of infusion.

**BMS CA225004 Summary:** Cetuximab AUC increased in a greater than dose proportional manner, while increases in C<sub>max</sub> were dose-proportional. CL decreased with increasing dose up to 250 mg/m<sup>2</sup> and was constant at doses of 250 and 400 mg/m<sup>2</sup>. Values for V<sub>ss</sub> remained constant over the dose range tested.

**Table 10. BMS CA225005 (Mean±SD) (Process/Batch #, — 01C00010, 01C00098, and 02C00063)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Dose (mg/m <sup>2</sup> )					
50 (n=5)	22.7±2.6	924±277	27.9±5.8	0.059±0.024	2.32±0.49
100 (n=6)	47.8±7.9	3040±718	43.6±13.8	0.034±0.008	2.20±0.37
250 (n=5)	149.4±19.6	13017±4027	71.6±21.6	0.021±0.006	2.09±0.14
400 (n=4)	221.2±81.7	23240±11469	100.5±15.4	0.021±0.013	2.96±1.47
500 (n=6)	244.5±69.1	23166±9369	79.3±38.9	0.024±0.009	3.11±0.63

Blood sampling for cetuximab concentration measurement were at pro-dose, 1, 1.58, 2.5, 3, 4, 6, 8, 24, 48, 96, 168, 264, 336, 432, and 504 h (Day 22) after the start of infusion.

**BMS CA225005 Summary:** Values for C<sub>max</sub> and AUC appeared to increase in a dose-related manner up to 400 mg/m<sup>2</sup> and then plateau at 500 mg/m<sup>2</sup>. CL decreased with dose up to 250 mg/m<sup>2</sup> and remained constant at higher doses.

**Table 11. IMCL CP02-9710 (Mean±SD) (Process/Batch #, — 970311, PS2 980077 and 980253)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-∞</sub> (µg.h/ml)	t <sub>1/2</sub> (h)	CL (L/m <sup>2</sup> /h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Dose (mg/m <sup>2</sup> )					
500/250 (n=6)	300.3±101.1	30713±12936	115.5±84.2	0.019±0.008	2.38±0.69
400/250 (n=35)	167.8±45.5	19263±6878	93.5±35.1	0.024±0.009	3.04±0.95

Blood sampling for cetuximab concentration measurement were at 0, and 1h following the end of the weekly infusion during the first course of therapy and at 24, 48, 72, 96, 120, and 144 h following the initial dose.

**IMCL CP02-9710 Summary:** Over the dose range studied, AUC appeared to increase in greater than dose-proportional manner. CL decreased and  $t_{1/2}$  increased with dose increasing.  $V_{ss}$  decreased with dose increasing although  $V_{ss}$  remained consistent with the vascular space at both doses.

**Table 12. EMR 62 202-012 (Mean±SD) (Process/Batch #, — 008416, 008459, 008500, 008861 and 008951)**

Parameter	$C_{max}$ ( $\mu\text{g}/\text{ml}$ )	$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{h}/\text{ml}$ )	$t_{1/2}$ (h)	CL ( $\text{L}/\text{m}^2/\text{h}$ )	$V_{ss}$ ( $\text{L}/\text{m}^2$ )
Dose ( $\text{mg}/\text{m}^2$ )					
400/250 (n=14/7)	152.9±38.4	22268±11052	118.6±42.4	0.020±0.006	2.07±0.55

Blood sampling for cetuximab measurement at Day 1 (0, 2h after stop of infusion), Day 8 (0 and after SOI), Day 15: 0, 1, 2, 6, 10, 24, 48 and 96h after SOI; Day 22: 0, 1, 2, 6, 10, 24, 48, 96 and 168h after SOI.

**EMR 62 202-012 Summary:** In this drug interaction study between cetuximab and irinotecan, cetuximab PK was similar to that seen in the dose escalation studies.

### Single Dose Data Summary

**Table 13. Single-Dose PK Parameters for Cetuximab Cross all Studies (mean±SD)**

Dose ( $\text{mg}/\text{m}^2$ )	N	$C_{max}$ ( $\mu\text{g}/\text{ml}$ )	$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{h}/\text{ml}$ )	$t_{1/2}$ (h)	CL ( $\text{L}/\text{h}/\text{m}^2$ )	$V_{ss}$ ( $\text{L}/\text{m}^2$ )
20	13	8.7±4.2	343±228	33.3±29.2	0.079±0.039	2.81±1.09
50	23	22.2±4.7	1031±440	32.3±9.8	0.059±0.028	2.49±0.70
100	52	46.8±11.6	2912±1060	44.8±12.8	0.039±0.015	2.48±0.91
200	14	102.4±29.4	9923±3226	79.8±19.6	0.020±0.010	2.31±1.05
250	8	140.2±19.6	12414±3332	65.9±18.8	0.021±0.005	2.17±0.16
300	4	133.2±47.7	16311±3786	90.4±13.8	0.019±0.005	2.52±0.49
400	56	184.5±54.6	21142±8657	97.2±37.4	0.022±0.009	2.91±0.90
500	20	283.8±84.1	32448±12880	119.4±76.9	0.018±0.008	2.63±0.66

**Figure 1. Plot of  $V_{ss}$  vs. Cetuximab Dose**

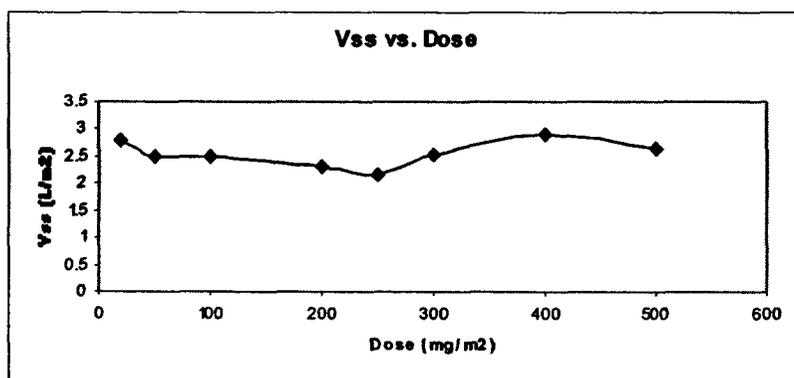
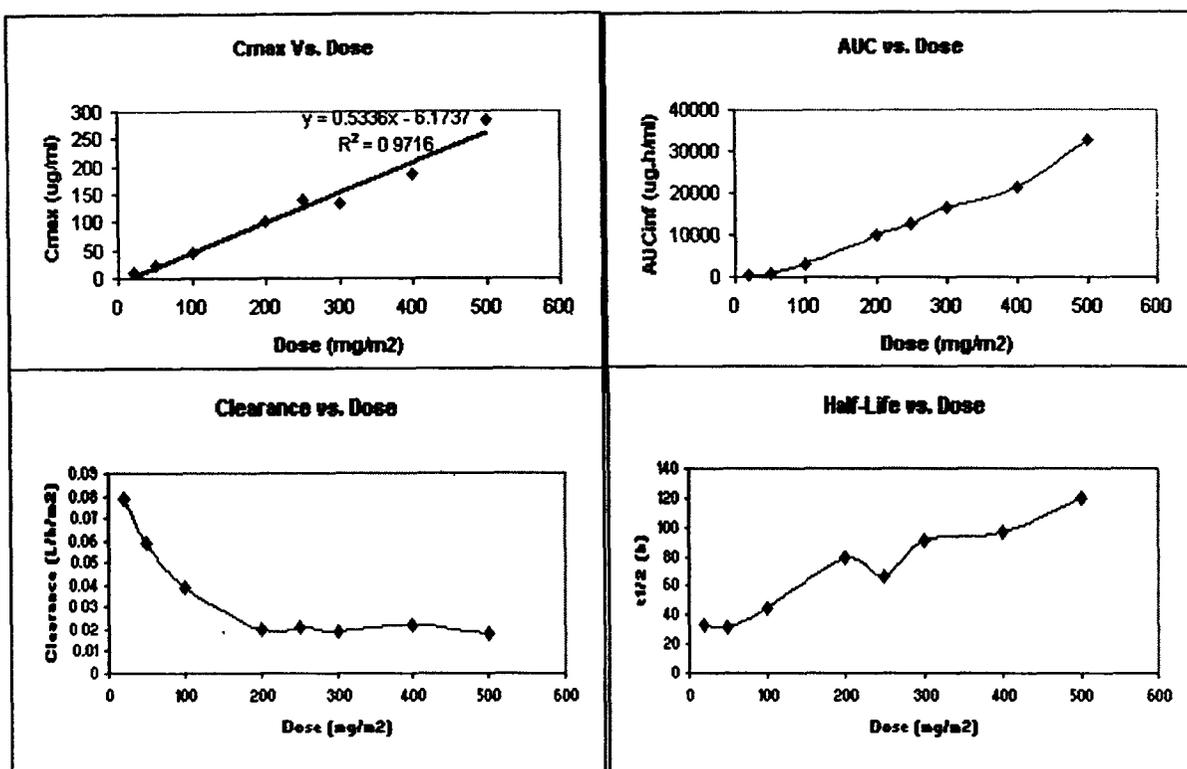


Figure 2. Plot of  $C_{max}$ , AUC, CL and  $T_{1/2}$  vs. Cetuximab Doses



### Conclusion

- The pharmacokinetics of cetuximab after single doses ranging from 5 to 500 mg/m<sup>2</sup> have been characterized in a broad range of studies and tumor types.
- Cetuximab exhibits nonlinear pharmacokinetics. AUC<sub>0-∞</sub> increased in a greater than dose proportional manner; clearance decreased and half-life increased with increasing of doses.
- As the dose of cetuximab increased from 20 to 200 mg/m<sup>2</sup>, the clearance decreased from 0.08 to 0.02 L/h/m<sup>2</sup>. At doses greater than 200 mg/m<sup>2</sup>, CL appeared to become constant. This plateau may be suggestive of a second, linear elimination pathway that becomes pronounced at doses above 200 mg/m<sup>2</sup>.
- The volume of distribution was observed to be independent of dose and consistent with a distribution of cetuximab in the vascular space.
- An apparent linear relationship between cetuximab dose and mean C<sub>max</sub> was observed.

### Target-Dose Studies (Multiple Doses)

In studies IMCL: CP02-9710, CP02-0141, EMR: 62 202-012, at the target dose of 400/250 mg/m<sup>2</sup>, cetuximab concentrations reached stable levels by the third weekly infusion with mean peak and trough concentrations ranging from 168-201 µg/ml and 54-64 µg/ml, respectively. In patients with metastatic CRC [IMCL: CP02-9923 and EMR: 62 202-007], cetuximab administered in combination with irinotecan, exhibited mean

trough levels ranging from 46-66 µg/ml over the course of therapy. When given as monotherapy, similar serum concentrations of cetuximab were observed.

**Table 14. IMCL CP02-9710 (Mean±SD)**

Week	(400/250 mg/m <sup>2</sup> )		Week	500/250 mg/m <sup>2</sup>	
	Peak (µg/ml)	Trough (µg/ml)		Peak (µg/ml)	Trough (µg/ml)
1 (n=35)	167.8±45.5	3.4±5.5	1 (n=6)	300.8±101.1	0.2±0.4
2 (n=38)	143.7±44.9	38.6±23.0	2 (n=4)	210.0±9.3	60.5±18.7
3 (n=32)	155.8±58.6	41.3±26.0	3 (n=5)	212.2±63.8	42.2±25.8
4 (n=35)	154.7±57.0	49.5±31.4	4 (n=3)	128.7±106.4	36.3±32.4
5 (n=35)	157.3±55.5	58.1±36.2	5 (n=6)	189.0±37.4	66.5±47.7
6 (n=29)	167.8±42.2	54.3±34.0	6 (n=4)	205.5±83.4	90.5±43.9
7 (n=26)	150.4±56.3	54.0±36.6	7 (n=4)	213.0±55.6	100.5±69.7
8 (n=23)	151.6±52.5	55.4±36.2	8 (n=4)	232.0±51.6	82.5±31.5

**Table 15. IMCL CP02-0141, EMR 62 202-007 and EMR 62 202-012 (Mean±SD)**

IMCL CP02-0141 (400/250 mg/m <sup>2</sup> )					
Week	Peak (µg/ml)	Trough (µg/ml)	Week	Peak (µg/ml)	Trough (µg/ml)
1 (n=53)	226.8±90.9	2.4±2.9	EMR 62 202-007		
4 (n=43)	195.4±65.8	56.7±29.9	1 (n=99)	182.8±44.4	1.7±17.2
6 (n=34)	201.0±69.8	64.1±29.3	7 (n=65)	ND	57.6±27.2
7 (n=23)	235.8±109.0	85.4±50.6	13 (n=34)	179.8±49.5	ND
13 (n=14)	212.7±61.0	88.6±30.4	EMR 62-202-012		
19 (n=12)	266.7±146.3	90.1±39.0	1 (n=7)	167.3±29.9	0.3±0.6
25 (n=6)	501.5±599.6	99.0±39.6	2 (n=7)	147.3±28.7	35.2±10.6
31 (n=2)	196±11.3	103.0±4.2	3 (n=6)	156.8±39.6	47.8±16.1

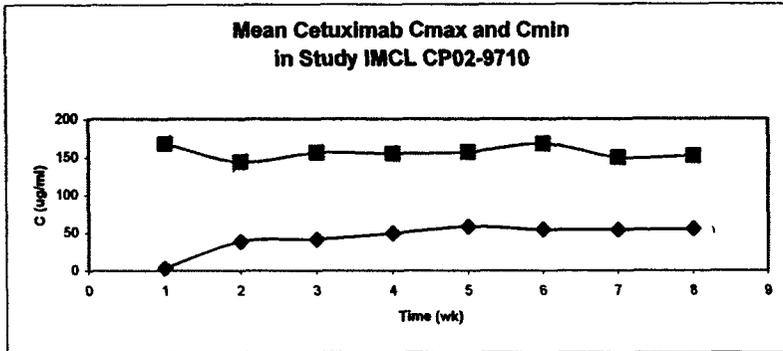
**Table 16. Mean Cetuximab Serum Peak and Trough Concentrations at the Target Dose (400 mg/m<sup>2</sup> initial and 250 mg/m<sup>2</sup> weekly) (mean±SD)**

Week	1	2	3	4	5	6	7	8
<b>CP02-9710</b>								
N	33	38	32	35	35	29	26	23
C <sub>trough</sub>	3.5±5.5	38.6±23.0	41.3±26.1	49.5±31.4	58.1±36.2	54.3±34.0	54.0±36.6	55.4±36.2
C <sub>peak</sub>	168±46	144±45	156±59	155±57	157±56	168±42	150±56	152±52
<b>CP02-0141</b>								
N	56			43	32		25	
C <sub>trough</sub>	2.4±2.9			56.7±30.0	64.1±29.3		85.4±506.6	
C <sub>peak</sub>	227±91			195±66	201±70		236±109	
<b>CP02-0144</b>								
N	25			19	16			
C <sub>trough</sub>	0			104.3±56.2	120.6±72.0			
C <sub>peak</sub>	305±112			310±98	323±126			
<b>EMR 62 2202-012</b>								
N	7	7	6	6				
C <sub>trough</sub>	0.3±0.6	35.2±10.6	47.8±16.1	52.2±20.7				
C <sub>peak</sub>	167±30	147±29	157±40					

**Table 17. Cetuximab Concentrations at Target Dose (400 mg/m<sup>2</sup> initial and 250 mg/m<sup>2</sup> weekly) (mean±SD)**

Study #	N	C <sub>trough</sub> (µg/ml)	C <sub>max</sub> (µg/ml)
CP 02-9813	19	29.6±14.0 (wk4), 24.1±17.4 (wk8), 41.5±32.7 (wk10)	
CP 02-9814	34	60.6±4.8, 52.6±22.4, 67.2±37.6, 41.4±10.2, 55.5±36.5	
CP 01-9816	104	41.4-55.1	
CP 02-9923	136	39.7-65.3	
CP 02-0038	30	56.6-101.2	
CP 02-0141	57	56.7-103.0	
EMR 62 202 007 292		55.0±29.8, 63.3±31.0, 70.6±39.4	190.3±64.6, 180.2±60.6

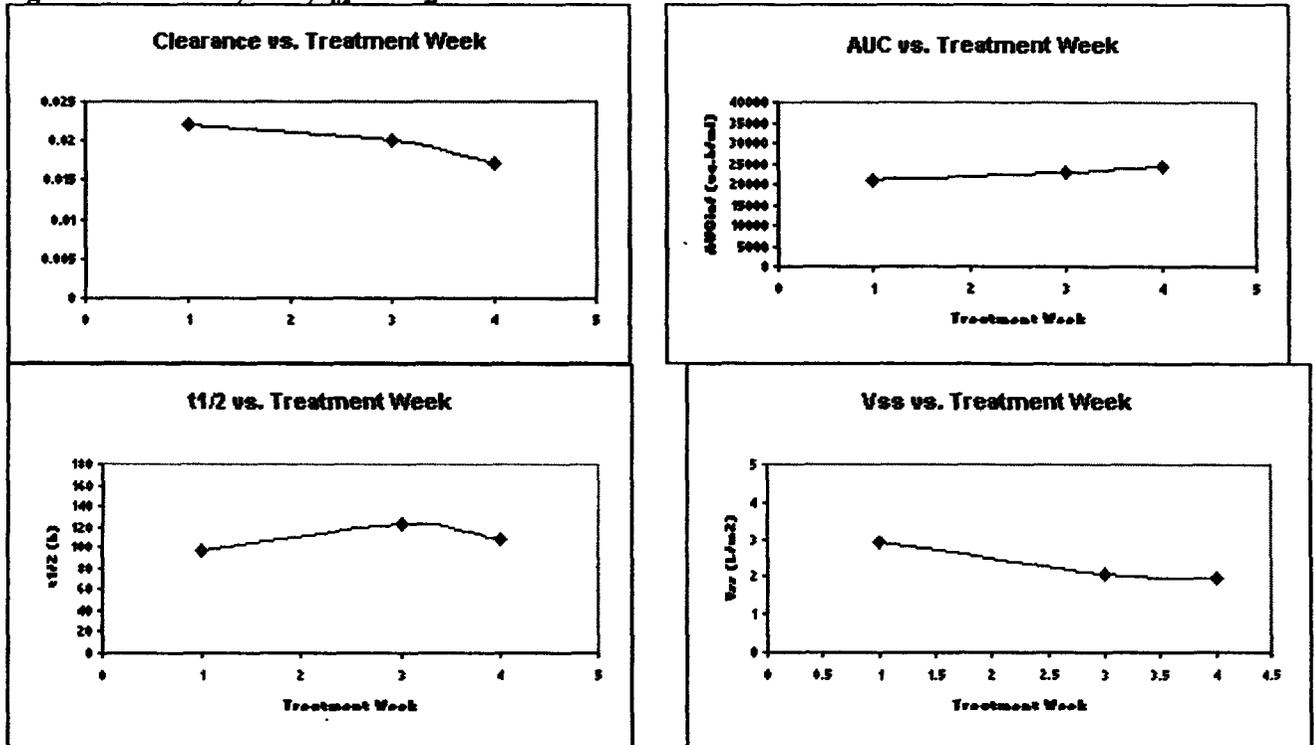
**Figure 3. Plot of C<sub>max</sub> and C<sub>trough</sub> vs. Time**



**Table 18. Comparison of PK Parameters in Multiple Dose Studies at the Target Dose (400 mg/m<sup>2</sup> initial [week 1], 250 mg/m<sup>2</sup> weekly) (mean±SD)**

Parameter	CL (L/h/m <sup>2</sup> )	AUC (µg.h/ml)	t <sub>1/2</sub> (h)	V <sub>ss</sub> (L/m <sup>2</sup> )
Week 1 (N=53)	0.022±0.009	21143±8657	97.2±37.4	2.91±0.90
Week 3 (N=8)	0.020±0.006	22723±10313	123.2±41.4	2.08±0.52
Week 4 (N=13)	0.017±0.006	24329±11202	108.1±29.3	1.99±0.59

**Figure 4. Plot of CL, AUC, t<sub>1/2</sub> and V<sub>ss</sub> vs. Time**



## Conclusion

- After administration of the target dose of 400/250 mg/m<sup>2</sup>, cetuximab peak and trough concentration were comparable across studies.
- Reasonably constant cetuximab peak and trough concentrations were generally reached within 3 to 5 weeks after the initiation of treatment and were maintained during later stages of the treatment.
- Available data indicate that the PK of cetuximab appears to remain unchanged for up to 4 weeks.

## Population Pharmacokinetic Evaluation

A comparison of the derived PK parameters from the non-compartmental analysis and the retrospective pooled population PK analysis was performed. A concentration-dependent decrease in CL was observed in the population PK analysis, similar to that observed in the non-compartmental analysis. The simulations indicated that at concentrations equal to the peak concentrations observed following single infusions of 250, 400 and 500 mg/m<sup>2</sup>, CL for cetuximab ranged from 0.01-0.012 L/h/m<sup>2</sup>, which is in reasonable agreement with CL values obtained in the non-compartmental analysis (0.02 L/h/m<sup>2</sup>).

## Pharmacokinetics in Special Populations

No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted. A population PK model analysis was used to investigate the potential effects of selected covariates including, hepatic and renal function, gender, race, weight, body surface area, and age on cetuximab pharmacokinetics. None of these covariates appeared to have a statistically significant effect on cetuximab PK, suggesting that dose adjustments are not needed for these groups. However, a gender difference was seen, with females exhibiting a 26% lower intrinsic cetuximab clearance. This difference did not appear to be clinically significant or necessitate any dose modification.

**Table 1. Summary of Demographic Characteristics of the Patient Population Used in the Population Pharmacokinetic Analysis**

Age (yr)	Weight (kg)	BSA (m <sup>2</sup> )	Gender (M/F)	Race (W/B/A/H/O)
59 (22-88)	73.5 (36.8-167)	1.85 (1.26-2.73)	578/328	821/45/18/14/8
Hepatic Status (N/Mil/Mod/S)		Renal Status (N/Mil/Mod/S)		
835/23/24/14		564/289/49/4		
Concomitant Medication (N)				
None (290) Radiation (33) Cisplatin (135) Paclitaxel (12) Doxorubicin (366) Gemcitabin (34)				
Primary Cancer Type (N)				
Bladder (5) Breast (13) Esophagus (1) Head and Neck (173) Kidney (55) Non small cell lung (16)				
Ovarian (7) Pancreas (39) Prostate (43) Colorectal (526) Gastric (1) Melanoma (2) Other (16)				
Unknown (9)				

The primary purpose of the population pharmacokinetic analysis was to define a model describing the pharmacokinetics of cetuximab following intravenous infusion and to identify sources of PK variability.

Creatinine clearance (CRCL), derived from serum creatinine data using the Cockcroft-Gault formulae, was included in the datasets as an indicator of renal function (RENL). The following biochemical markers for hepatic function (HEP) were also included in the dataset: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total albumin (ALB) and total bilirubin (BILI).

The EGFR status of patients, the best tumor response as assessed by independent review for three of the studies (EMR 62 202-007 and Studies IMCL CP02-0038, 0141 and 9923), were also included in the dataset as categorical variables. The corresponding physicians' assessment of response for Studies IMCL CP02-0038 and Studies CA225004 and CA225005, in addition to the above three studies was also included in the dataset.

The cetuximab lot administered in each of the studies was also included in the dataset (LOT). If more than one lot used in the study, the first lot number was used. Due to the large number of different lots used in the studies, a second variable specifying the process by which each lot was manufactured was also used (PROC) and used as a potential covariate.

Two variables denoting the presence or absence of skin rash (SK1, SK2) were also included in the dataset. If COSTART = {Acne, rash, maculopapular rash, pustular rash} and PK sample data between onset and resolved date and relationship to study drug are either definite/possible/probable, SK1=1, otherwise SK1=0. If COSTART = {vasodilation, dry skin, skin disorder, pruritus, urticaria, vesiculobullous rash, purpuric rash, petechial rash, petechia, photosensitivity reaction, nail disorder} and PK sample data between onset and resolved date and relationship to study drug are either definite/possible/probable, SK2=2, otherwise SK2=0.

A two-compartment model with saturable elimination was used to describe the available cetuximab PK data. The  $V_c$  and  $V_p$  were estimated to be 4.49 L and 4.54 L, respectively, with a 27% reduction in the typical value of the  $V_c$  in females. The intercompartment flow,  $Q$ , was estimated to be 0.0493 L/h. The typical value of  $V_{max}$  for males was 5.40 mg/h with a 26% reduction in females. The typical value of  $K_m$  was 91.5  $\mu\text{g/ml}$ , giving an intrinsic clearance from the saturable pathway of 0.059 L/h in males and 0.043 L/h in females. The sponsor claims that this difference (26%) was within the variability of the data and would not be expected to be clinically relevant.

The various processes by which the different lots of cetuximab were made did not influence the resulting pharmacokinetics, however, it should be noted that there were numerous lots that were used in these 19 studies. These lots were sub-categorized into 6 processes (PROC) in order to better delineate any potential effects.

There were no other patient covariate factors that appeared to have had a significant impact on the pharmacokinetics of cetuximab or that would result in any dosage adjustments. Specifically, neither renal impairment nor hepatic impairment resulted in any changes in the PK of cetuximab. The subject numbers were small for hepatic and renal impairment (N/Mil/Mod/S 835/23/24/14) and renal impairment (N/Mil/Mod/S,

564/289/49/4). The interpatient variability in the PK parameter estimates was low and ranged from 6 to 40%.

***Inter-Individual Variability in PK Data***

The integrated PK analysis investigated the inter-individual variability associated with the PK data. The population PK analysis identified sex as the only covariate, although this covariate did not require dose adjustment. The interpatient variability in the pharmacokinetic parameter estimates was low and ranged from 6 to 40%. This suggests that cetuximab concentrations can be reliably predicted from the administered dose.

***Drug Metabolism and In vitro Drug-Drug Interaction Studies***

No studies on the metabolism of cetuximab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, “the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids” and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No in-vitro drug-drug interaction studies have been performed.

***Drug-Drug Interaction Studies***

A formal drug-drug interaction study (EMR: 62 202-012) of cetuximab and irinotecan did not reveal any evidence of a PK interaction between these agents. In addition, the possible impact of radiation, cisplatin, paclitaxel, doxorubicin, gemcitabin, and irinotecan on the PK of cetuximab was evaluated in the population PK analysis. This analysis demonstrated that these concomitant therapies did not have a demonstrable influence on the PK characteristics of cetuximab.

EMR 62 202-012 was performed to investigate potential interactions of the target dose of cetuximab with irinotecan and its active metabolites SN-38 and SN-38 — Blood sampling for cetuximab measurement were collected at Day 1 (0, 2h after stop of infusion), Day 8 (0 and after SOI), Day 15: 0, 1, 2, 6, 10, 24, 48 and 96h after SOI; Day 22: 0, 1, 2, 6, 10, 24, 48, 96 and 168h after SOI.

**Table 1. Study Design**

	Irinotecan Single dose 350 mg/m <sup>2</sup>	Cetuximab 400 mg/m <sup>2</sup>	250 mg/m <sup>2</sup>	PK Data
Group A (n=6)	Weeks 1 and 4	Week 2	Weeks 3 and 4	Irinotecan PK
Group B (n=8)	Week 4	Week 1	Weeks 2, 3, and 4	Cetuximab PK

**Table 2. PK parameters of Irinotecan in Group A (N=6, M/F 3/3) (mean±SD)(median)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>0-4</sub> (µg.h/ml)	AUC <sub>0-∞</sub> (µg.h/ml)
WK 1 (alone)	8129±2882 (7071)	42792±22277 (33064)	44243±23683 (33857)
WK 4 (combo)	6783±1293 (6474)	39051±16852 (37598)	40394±18365 (38251)
WK 4/WK 1	90±29% (87%)	96±22% (97%)	96±21% (98%)
Parameter	t <sub>1/2</sub> (h)	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )
WK 1 (alone)	9.8±2.6 (9.9)	9.7±4.2 (10.4)	83±21 (82)
WK 4 (combo)	9.8±2.0 (9.4)	10.0±4.3 (9.2)	85±15 (84)
WK 4/WK 1	102±16% (102%)	107±26% (99%)	106±21% (109%)

**Table 3. PK Parameters of Cetuximab in Group B (N=7, M/F 3/4) (mean±SD)(median)**

Parameter	C <sub>max</sub> (µg/ml)	AUC <sub>t</sub> (µg.h/ml)	t <sub>1/2</sub> (h)
WK 3 (alone)	153±38 (138)	13039±4783 (12874)	119±42 (100)
WK 4 (combo)	162±43 (168)	14923±5029 (16183)	117±32 (106)
WK 4/WK 3	106±11% (104%)	117±14% (108%)	107±38% (103%)
Parameter	CL (L/h/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )	
WK 3 (alone)	0.020±0.006 (0.019)	2.07±0.55 (1.95)	
WK 4 (combo)	0.018±0.007 (0.015)	1.89±0.55 (1.89)	
WK 4/WK 3	91±8% (92%)	92±13% (93%)	

**Conclusions:**

- The PK parameter values for irinotecan at Week 1 were similar to those at Week 4, suggesting the absence of a PK interaction with cetuximab. An attempt was made to characterize the PK profile of the irinotecan metabolites SN-38 and SN-38' but no meaningful results were obtained.
- The PK parameter values for cetuximab at Week 3 were similar to those at Week 4, suggesting the absence of a PK interaction with irinotecan.

**Pharmacodynamics**

A single PK/PD study (CA115005) was conducted to characterize the effects of single doses of cetuximab (50-500 mg/m<sup>2</sup>) on expression and saturation of EGFR, and on other downstream signaling pathways, in normal skin and in tumor tissue of cancer patients. EGFR analysis in skin biopsy samples demonstrated a decrease in EGFR protein levels across the 250-500 mg/m<sup>2</sup> dose range, with a maximal effect occurring at 400 mg/m<sup>2</sup>, and an increase in EGFR protein levels across the 50 and 100 mg/m<sup>2</sup> doses. Single-dose pharmacodynamic effects in EGFR, p-EGFR, p-MAPK, Ki67 and P27 were not seen in tumor samples.

Two additional studies were performed to evaluate the pharmacodynamics of cetuximab: IMCL CP02-9608 and BMS CA225005.

**Table 1. IMCL 9608 Study Design (N=12)**

Dose regimen (cetuximab Initial/maintenance, mg/m <sup>2</sup> ):	100/100, 400/250, 500/250
Tumor tissue sampling time: baseline, 24 hrs after 1 <sup>st</sup> infusion and 24 hrs before 3 <sup>rd</sup> infusion	

All tumor specimens at each time point were stained with hematoxylin and eosin to evaluate viability and tumor cells. Tumor EGFr binding was assessed using immunohistochemistry (N=8), analysis of residual tyrosine kinase activity (N=4), and immunoblot analysis of bound EGFr (N=5). Results of immunohistochemistry indicated saturation by cetuximab of tumor EGFr of between 10 and 90% depending on dose.

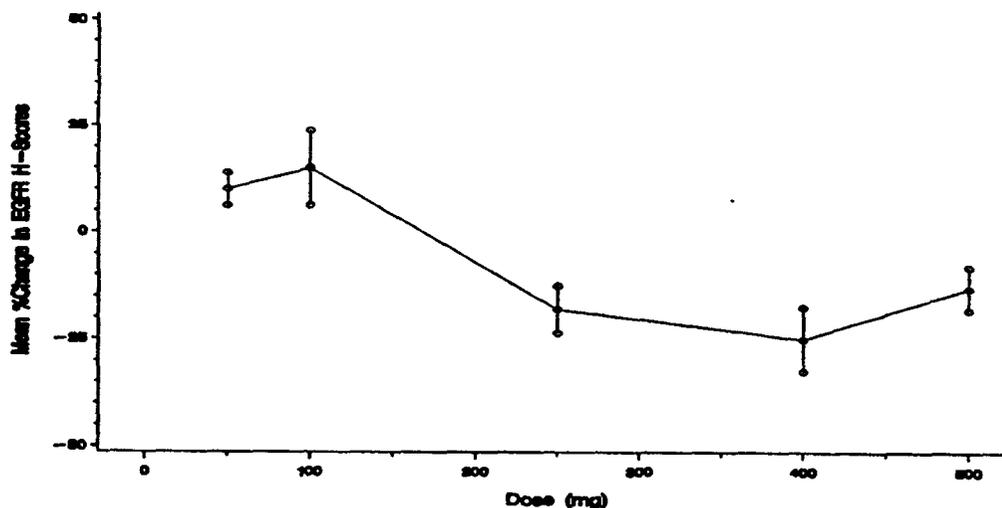
**Table 2. BMS Study Ca225005 Study Design (N=26)**

Dose regimen: cetuximab single dose (mg/m<sup>2</sup>) 50, 100, 250, 400, 500  
 Biopsies: 5 skin biopsies (Days 0, 2, 8, 15, 22) and 2 tumor biopsies (Days 0, 8)

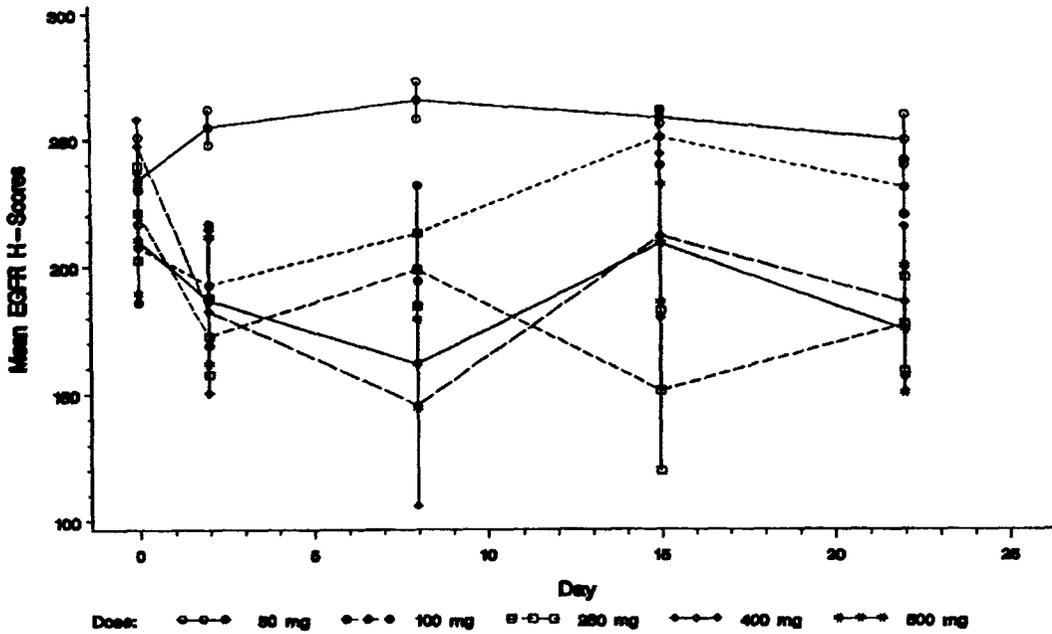
Quantitative immunohistochemical analysis was performed on the biopsies taken after a single dose of cetuximab for the following parameters: EGFr and activated EGFr (p-EGFr), cell cycle proteins ( ——— ), and signal transduction (nitrogen-activated protein kinase [ ——— ] and activated [ ——— ])

**Results:** Immunohistochemical analysis in skin biopsies obtained after a single cetuximab dose, demonstrated a dose dependent pharmacodynamic effect. Single doses  $\geq 250$  mg/m<sup>2</sup> produced decrease in EGFr protein levels with maximal decreases occurring at 400 mg/m<sup>2</sup>, whereas at doses below 250 mg/m<sup>2</sup>, slight increases in EGFr protein levels were noted. Maximal inhibition occurred approximately at 8 days after biopsy, with a return to approximate baseline EGFR protein levels at Day 15. P-EGFr expression demonstrated a similar dose- and time-dependent regulation in skin with increases of protein expression seen across the 50 to 500 mg/m<sup>2</sup> dose range and a maximal effect occurring at 250 mg/m<sup>2</sup> on Day 2.

**Figure 1. Mean  $\pm$  SE Percentage Change in EGFr (Skin Biopsies) H-Score, Compared to Baseline, as a Function of Cetuximab Dose**

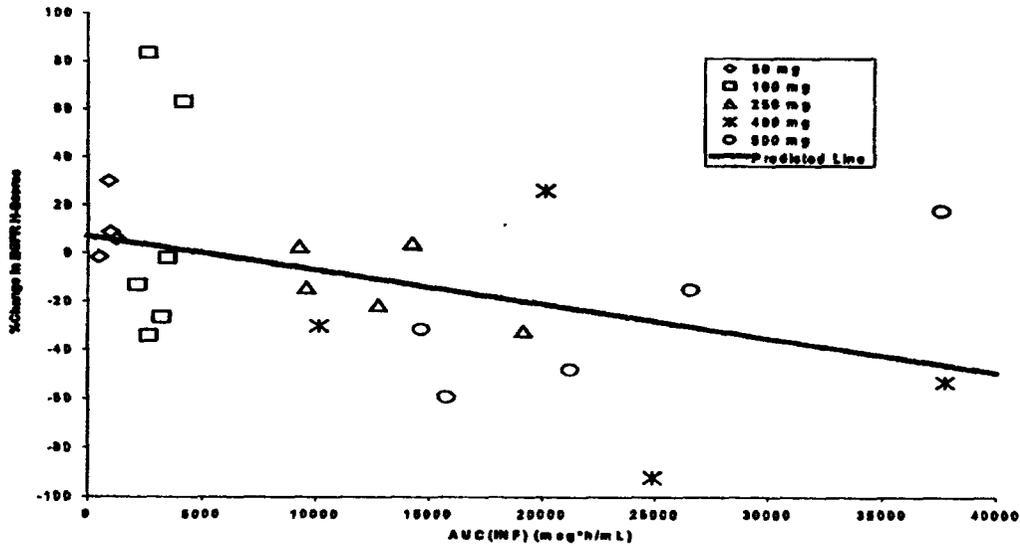


**Figure 2. Mean±SE Change in EGFr (Skin Biopsies) H-Score, Compared to Baseline, as a Function of Cetuximab Dose and Time**



Pharmacokinetic/pharmacodynamic relationships were analyzed by comparing change in marker expression in skin biopsies to mean  $AUC_{0-\infty}$  for all patients. The percentage change in EGFr expression on Day 8 in skin biopsies, compared to baseline was plotted as a function of exposure to cetuximab as measured by  $AUC_{0-\infty}$ .

**Figure 3. Percent Change in EGFr (Skin Biopsies), Compared to Baseline, as a Function of  $AUC_{0-\infty}$**



**Table 3. PD Markers (Skin Biopsies)**

Drug exposure	PD marker	Effect	Time to maximum effect	Time to return to baseline
Single doses				
Doses $\geq 250$ mg/m <sup>2</sup>	EGFr Protein Levels	↓, maximum ↓ at 400 mg/m <sup>2</sup>	Day 8	Day 15
<250 mg/m <sup>2</sup>		Slightly ↑		
Doses 50-500	p-EGFr expression	↑, maximum ↑ at 250 mg/m <sup>2</sup>	Day 2	
AUC <sub>0-∞</sub>	EGFr Protein Levels	↓, maximum ↓ at 10,000 μg.h/ml (doses of at least 200 mg/m <sup>2</sup> )		
	p-EGFr expression	Slightly ↑		
Doses 50-500	Cell cycle proteins p27, Ki67	Upregulation, independent of dose and exposure unaffected		
	MAPK	inadequate staining by immunohistochemistry		
	Expression of p-MAPK	Time-dependent down regulation	Days 8 and 15	Day 22
		No trend with regards to cetuximab dose or exposure		

Cetuximab-related changes in EGFr and p-EGFr in tumor biopsies showed inconsistent trends across dose and time making the results from these markers inconclusive. Cetuximab on p27 in tumor biopsies was variable and inconclusive. Ki67 expression appeared unaffected in both skin and tumor biopsies by single-dose cetuximab. Tumor expression of p-MAPK was variable and inconclusive.

Increasing exposure to cetuximab, as measured by AUC<sub>0-∞</sub>, corresponded to decreases in EGFr expression and increases in p-EGFr in skin biopsies, Maximum percent change in EGFr H-score occurred at AUC values greater than 10,000 μg.h/ml, corresponding to doses of at least 200 mg/m<sup>2</sup>.

An attempt was made to measure EGFr saturation by immunohistochemistry. However, this method did not prove to be a suitable method due to analytical limitations.

#### **Conclusions:**

- EGFR analysis in skin biopsies appeared to reveal a decrease in EGFr protein levels across the 250-500 mg/m<sup>2</sup> dose range, with a maximal effect reached at a dose of 400 mg/m<sup>2</sup>. An increase in EGFR protein levels appeared to occur at the 50 and 100 mg/m<sup>2</sup> doses.
- 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.

#### **Exposure-Response**

The potential relationship between cetuximab exposure and the response as assessed by independent review and physician's assessment was explored for Studies 007, 0141 and 9923. In these studies, all patients had colorectal cancer and received an initial dose of 400 mg/m<sup>2</sup> followed by weekly doses of 250 mg/m<sup>2</sup>. 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 although female patients had a 26% lower cetuximab clearance compared to that of male patients.

### **Dose-Finding Rationale**

A therapeutically useful dose of cetuximab was hypothesized to be one that maintained continuous occupancy of EGFr *in vivo*, resulting in prolonged blockade of EGFr-dependent signal transduction cascade. In the early dose-escalation studies examining dose between 5-500 mg/m<sup>2</sup>, an acceptable safety profile was seen up to and including 400 mg/m<sup>2</sup> weekly dose. Doses of 500 mg/m<sup>2</sup> produced an unacceptable high incidence of skin toxicity; therefore, only doses below 500 mg/m<sup>2</sup> were evaluated in further clinical development. Evaluation of clinical data at well-tolerated doses between 5 and 400 mg/m<sup>2</sup> demonstrated that efficacy was observed at doses between 250 and 400 mg/m<sup>2</sup>.

Across the safety and efficacious dose range of 250-400 mg/m<sup>2</sup>, the median half-life ranged between 64-87 hours. The estimated half-life at these doses would support a weekly dosing regimen because patients would be expected to have measurable cetuximab concentrations throughout the dose interval.

In the 19 studies where concentration-time data were acquired, cetuximab displayed nonlinear pharmacokinetics in which exposure increased in a greater than dose proportional manner. Also, in these studies, CL of cetuximab decreased with increasing dose. As dose of cetuximab increased from 20 to 200 mg/m<sup>2</sup>, CL decreased from 0.08 to 0.02 L/h/m<sup>2</sup>. At doses greater than 200 mg/m<sup>2</sup>, CL appeared to become constant. This is suggestive of at least 2 elimination pathways; one saturable at doses below 200 mg/m<sup>2</sup> and another being nonsaturable at doses up, at least 500 mg/m<sup>2</sup>. At the target dose of 400/250 mg/m<sup>2</sup>, first-order kinetics are observed indicating predictable PK within this dose range. In addition, the lower, as well as constant, CL values at doses above 200 mg/m<sup>2</sup> will maintain therapeutic levels for longer periods of time.

A pharmacodynamic analysis of cetuximab on EGFr protein demonstrated maximal inhibition of EGFr expression across the 250-500 mg/m<sup>2</sup> dose range. At doses below 250 mg/m<sup>2</sup>, however, an increase in EGFr protein expression was observed, suggesting that therapeutic activity would be best maintained with dose at or above 250 mg/m<sup>2</sup>. An initial dose of 400 mg/m<sup>2</sup> followed by a weekly dose of 250 mg/m<sup>2</sup> was demonstrated to be well tolerated and efficacious across multiple studies. The pharmacokinetic behavior of cetuximab together with its pharmacodynamic activity on the EGFr is further supportive of both dose and regimen.

### **Immunogenicity**

Cetuximab has the potential to induce an immune response. During the cetuximab clinical development program, patient sera were monitored for induction of an anti-cetuximab or human-chimeric antibody (HACA) response. Patients were evaluable for HACA responses if they had both pre- and post-baseline samples available for analysis. The results of the HACA analyses in 17 clinical studies are summarized in Table 3.7.

Low titer, HACA was detected in 3.7% of evaluable patients with a median time to onset of 44 days. Limited clinical data do not indicate that HACAs have a neutralizing effect on the activity of cetuximab. No relationship between the presence of these antibodies and discontinuation of therapy was observed. At least

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***Anti-cetuximab Assay***

Two assays were used for the determination of anti-cetuximab responses in cetuximab clinical trials. The assay used by ImClone to determine anti-cetuximab reactivity was a non-species-specific, double-antigen, radiometric assay specific for cetuximab. In the Merck studies a sandwich ELISA was used to determine the anti-cetuximab responses. Both assays are based on a similar principle that relies on capture and detection of anti-cetuximab antibodies by cetuximab itself. As these assays may be sensitive to the presence of excess amount of free cetuximab in the clinical samples, anti-cetuximab responses should be interpreted with caution. In order to assess any potential interfering effects of free cetuximab, samples were monitored for both cetuximab and anti-cetuximab reactivity.

Blood samples were drawn prior to the initial cetuximab infusion (pre-treatment sample) and prior to cetuximab infusions during subsequent courses of therapy. In some studies, blood samples were drawn 4 to 16 weeks following the final infusion of cetuximab and in EMR 62 202-007, several patients had blood drawn 6 weeks following the final infusion to provide samples with minimal levels of cetuximab.

**Table 1. Criteria of Positive for Anti-Cetuximab Response**

<i>ImClone assay:</i>	a post-baseline response >10 ng/ml <sup>125</sup> I cetuximab binding, and the post-baseline value >twice the baseline value with at least 2 consecutive determinations.
<i>Merck assay:</i>	OD value >0.100 OD and at least 3-fold of the pretreatment value.

**(a) Incidence of Anti-Cetuximab Response by Study**

**Table 2. Maximal Anti-Cetuximab Level, Time to Onset and Duration of Anti-Cetuximab Response in Patients Positive for an Anti-Cetuximab Response (Median with range)**

Weekly Dose (mg/m <sup>2</sup> )	5	20	100	250	Overall
N	3	3	2	12	20
Time to Onset (D)	36-57	8-78	16-22	8-281	44
Time Post Infusion (D)	8	8	9	8-130	9
Duration (D)	35-unknown	6-unknown	21-unknown	64-unknown	28
R <sub>max</sub> (ng/ml)	—————>				
C <sub>max</sub> (µg/ml)	—————>				

Of 614 patients examined, 534 patients were evaluable and 20 patients exhibited anti-cetuximab responses yielding an overall incidence of 3.7% (0% to 23.1%). The incidence of an anti-cetuximab response from trial to trial did not appear to follow a clear identifiable trend. Overall, the mean and median time to onset of observed anti-cetuximab response was 81 and 44 days (range: 8 to 281 days), respectively. The time to onset did not appear to correlate with maximum level of response.

**(b) Anti-Cetuximab Response as a Function of Weekly Cetuximab Dose**

**Table 3. Anti-Cetuximab Response as a Function of Weekly Dose of Cetuximab**

Dose (mg/m <sup>2</sup> )	5	20	50	100	200	250	300	400	Overall
Treated/Tested	17/13	26/14	19/15	42/34	30/25	789/499	8/5	14/9	945/614
Evaluable/Positive	10/3	13/3	9/0	29/2	21/0	442/11	5/0	5/1	534/20
Response Incidence (%)	30.0	23.1	0.0	6.9	0.0	2.5	0.0	20.0	3.7

The results of the following summary table indicates that the incidence of an anti-cetuximab response appeared to decrease with increasing weekly cetuximab dose. Studies with weekly dose >100 mg/m<sup>2</sup> appeared to be associated with the lower levels of an anti-cetuximab response although the number of patients treated with doses <100 mg/m<sup>2</sup> was small.

**(c) Anti-Cetuximab Response as a Function of Concomitant Chemotherapy**

**Table 4. Anti-Cetuximab Response as a Function of Concomitant Chemotherapy**

Concomitant Agent	Treated	Tested	Evaluable	Positive	Incidence (%)
None (Monotherapy)	234	158	141	6	4.3
Cis- or carboplatin	179	146	121	9	7.4
Paclitaxel	12	10	8	0	0.0
Doxorubin	36	35	31	1	3.2
Irinotecan	443	225	198	4	2.0
Gemcitabine	41	40	35	0	0.0
Overall	945	614	534	20	3.7

Patients receiving paclitaxel or gemcitabine did not exhibit an anti-cetuximab response. Patients receiving irinotecan, doxorubicin, or cis/carboplatin exhibited a 2.0, 3.2 and 7.4% anti-cetuximab incidence, respectively. Patients who did not receive concomitant chemotherapy (Monotherapy) exhibited an anti-cetuximab incidence within this range (4.3%). Patients receiving irinotecan-based combination therapy exhibited a lower incidence than that of the patient population overall. There is no indication that concomitant chemotherapy influenced the development of an anti-cetuximab response, however, the number of patients are too small to draw any conclusions.

**(d) Anti-Cetuximab Response as a Function of Duration of Cetuximab Treatment**

**Table 4. Anti-Cetuximab Response as a Function of Duration of Cetuximab Treatment**

Duration of Treatment	Treated		Tested		Evaluable		Positive		Incidence (%)	
	Target Dose	Other Dose	Target Dose	Other Dose						
≥8 weeks	292	99	168	74	125	63	7	5	5.6	7.9
>8-24 weeks	272	67	173	64	164	52	3	3	1.8	5.8
>24 weeks	194	21	114	21	109	21	2	0	1.8	0.0
Total	758	187	455	159	398	136	12	8	3.0	5.9
Overall	945		614		534		20		3.7	

Noted that as HACA samples were not taken at the end of treatment for all patients the data should be interpreted with caution. There was a general trend for anti-cetuximab incidence to decrease with increasing duration of therapy. Patients who received cetuximab for 8 weeks or less exhibited an anti-cetuximab incidence (12 of 188, 6.4%)

approximately twice that of those receiving it for 8 to 24 weeks (6 of 216, 2.8%) and approximately 4-fold that of those receiving cetuximab for more than 24 weeks (2 of 130, 1.5%). Patients who received the target dose (400/250 mg/m<sup>2</sup>) cetuximab regimen followed a similar trend. The incidence for 8 week or less (7 of 125, 5.6%) was 4-fold that of those for 8-24 weeks (3 of 164, 1.8%) and for >24 weeks (2 of 109, 1.8%). Overall, patients receiving the target dose regimen had an anti-cetuximab incidence of 3.0% (12 of 398).

**(e) Anti-Cetuximab Response and Allergic Reactions**

The occurrence of an allergic or anaphylactic reaction did not appear to correlate with the development of an anti-cetuximab response. Of the 20 patients with positive anti-cetuximab response, only 1 patient (Patient 061319 in IMCL CP02-9813) exhibited an allergic reaction. The physician assessment of this allergic reaction indicated that it was unrelated to cetuximab and was a response to oxycodone. Anti-cetuximab antibodies were not detected until 12 to 16 weeks following the patient's last infusion of cetuximab.

In Study EMR 62 202-007, patients with a detectable anti-cetuximab response experienced adverse events associated with inflammatory or hypersensitivity reactions (e.g., chills, fever). However, these adverse events were not restricted to patients exhibiting anti-cetuximab responses.

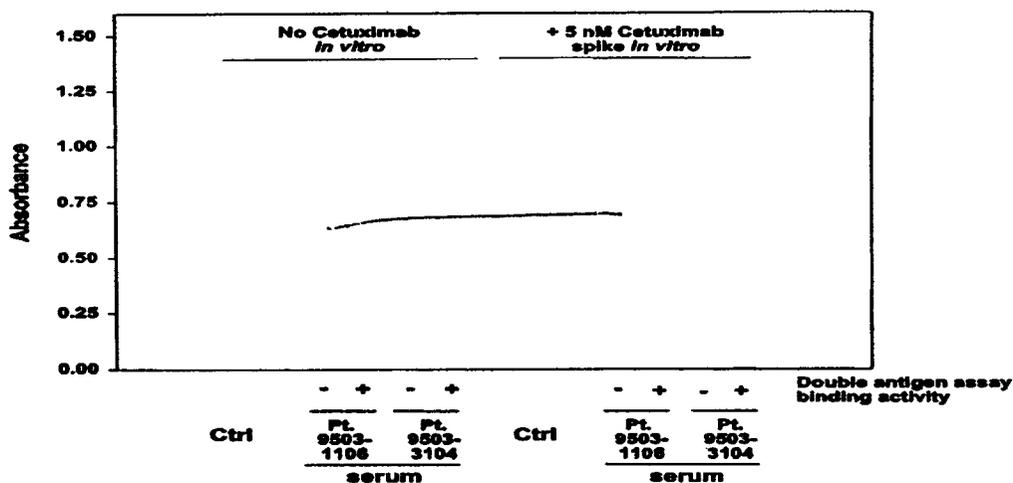
**(f) Neutralization of Cetuximab and Impact on PK by Anti-Cetuximab Antibodies**

The magnitude of an anti-cetuximab response is quantified by determine the amount of radiolabeled cetuximab than can bind to captured serum anti-cetuximab antibodies. Generally the anti-cetuximab antibodies in serum samples were found to bind less than 350 ng/ml of cetuximab, with most anti-cetuximab values falling in the range of — ng/ml or below. The determination of the absolute amount of cetuximab protein bound is based on the specific activity of the radiolabeled cetuximab tracer.

In the cetuximab clinical development program, 2 patients from a single study (IMCL CP02-9503) had a significantly elevated anti-cetuximab antibody response ( ~~\_\_\_\_\_~~ ). Their blood samples allowed evaluation of the ability of the induced anti-cetuximab antibodies to neutralize the biological activity of cetuximab *in vitro*.

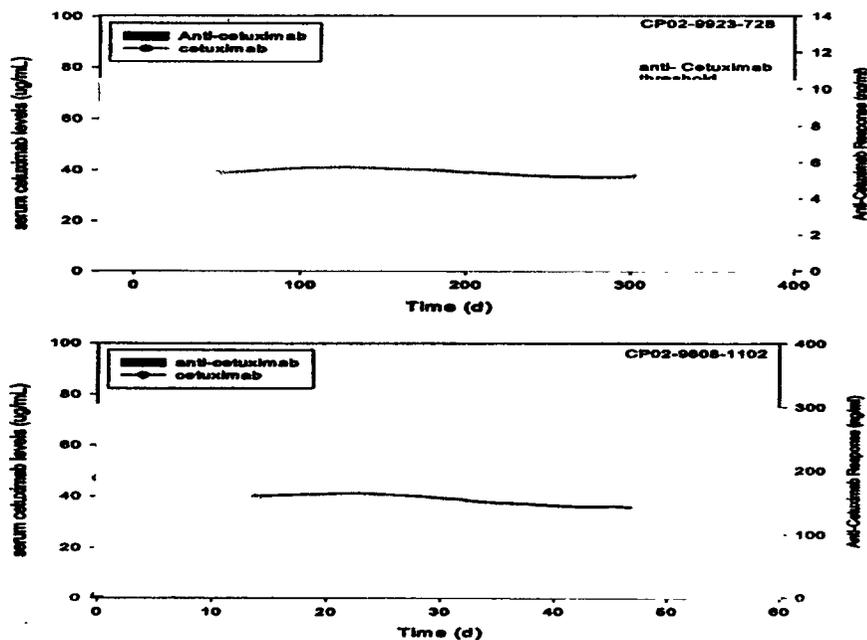
The neutralization experiments utilized DiFi CRC cell lines that depend on epidermal growth factor (EGF) for proliferation. Cetuximab inhibits proliferation of these cells. Patient sera incubated with cetuximab inhibited proliferation of DiFi CRC cells to the same extent as cetuximab alone, suggesting that, in these 2 patients, the anti-cetuximab antibodies did not interfere with the ability of cetuximab to bind EGFr (i.e., they are non-neutralizing). The results demonstrate that an anti-cetuximab response might not be expected to alter the biologic activity of cetuximab *in vitro*.

**Figure 1. Sera from 2 Patients with High Anti-Cetuximab Activity do not Neutralize the Antiproliferative Activity of Cetuximab**



An anti-cetuximab antibody response could nevertheless alter cetuximab exposure via a PK interaction (via immune complex formation and/or altered clearance). To determine if an anti-cetuximab response might alter cetuximab bioexposure and clearance, an analysis was performed of serum cetuximab concentrations in individuals with anti-cetuximab antibodies. Among the 20 individuals with anti-cetuximab responses, only 2 had trough serum cetuximab levels that suggested a possible effect of the induced anti-cetuximab antibody on serum cetuximab concentration and clearance. Coincident with an increase in anti-cetuximab reactivity, levels of serum cetuximab decreased over time in both patients.

**Figure 2. Effect of Anti-Cetuximab Antibodies on Serum Cetuximab Levels in Patients CP02-9923-035728 (top) and CP02-9608-001102 (bottom)**



In Patient 001102 from IMCL CO-2-9608, a moderately strong anti-cetuximab response ( ) coincided with a marked decrease in serum cetuximab levels. Peak cetuximab concentrations following development of the anti-cetuximab antibody response were approximately 33% of the levels prior to the development of the anti-cetuximab antibody response. The patient did not exhibit a clinical response to cetuximab treatment. This single instance in which an anti-cetuximab response altered cetuximab serum levels occurred at a dose level of 100 mg/m<sup>2</sup> and not at the target dose.

In Patient 035728 from IMCL CP02-9923, the observed decrease was within the range of variability of cetuximab concentrations observed in the study population and thus may not be completely attributable to an anti-cetuximab response. The fact that anti-cetuximab levels are just above the positive threshold level supports the hypothesis that this decrease may be due to population variation and may not represent a true alteration of PK by an anti-cetuximab response. This patient had an objective partial response to cetuximab/irinotecan therapy suggesting that the anti-cetuximab antibody response may not have adversely affected the clinical outcome.

**Conclusion:**

- Overall, the incidence of anti-cetuximab response in patients receiving cetuximab was low (5.3%) and responses were typically of low titer.
- Although the data are limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or anti-tumor activity of the molecule.
- Allergic reactions in patients receiving cetuximab did not appear to correlate with the presence of an anti-cetuximab response.
- The data indicate an anti-cetuximab response may have an effect on cetuximab PK in 2 of 20 patients (one at 100 mg/m<sup>2</sup> and the other at target dose) that tested positive for an anti-cetuximab response. At the weekly target dose of 250 mg/m<sup>2</sup>, however there appears to be little impact on clinical outcome as the patient exhibited a clinical response to cetuximab.
- The low incidence of non-neutralizing anti-cetuximab antibodies, and the limited impact of antibody formation on cetuximab PK at the target dose suggest that anti-cetuximab antibodies will not affect the clinical application of cetuximab.

**General Biopharmaceutics**

The efficacy results from three clinical trials (EMR 62 202-007, IMCL-9923 and IMCL-0141) form the basis to support an accelerated approval of cetuximab for the proposed indication. The to-be-marketed product manufactured in Lonza facility is the clinical trial product.

The sponsor originally proposed to market the product manufactured in BB36 facility which was only used in the ongoing clinical trial IMCL-0144.

**Table 1. Product Lots Used in These Clinical Trials**

Trial Number	Product Lot Number	Manufacturing Sites
IMCL CP02-9923	980452, 990261, 990609, 990388, 990764, 990819, 000007, 00C00453, 01C00006, 01C00090, 00C00660, 00C00664, 01C00503	Lonza
IMCL CP02-0141	00C01178, 00C00010	Lonza
EMR 62 202-007	00C001178, 01C01178, 00C01178, 00C00453, 00C00006, 00C00010, 00C0090	Lonza
IMCL CP02-0144	02C00001B	BB36
<i>Other Trials</i>		
IMCL CP02-9710	970311, 980077, 980253	Lonza
EMR 62 202-012	008416, 008458, 008459, 008500, 008861, 008951	Lonza

The peak and trough concentrations measured in these clinical trials are summarized in the following tables:

**Table 2. Mean Cetuximab Serum Peak and Trough Concentrations ( $\mu\text{g/ml}$ ) at the Target Dose of  $400\text{mg/m}^2/250\text{mg/m}^2$  (mean $\pm$ SD)**

Week	1	2	3	4	5	6	7	13	
IMCL CP02-0141 (Irinotecan-refractory, Stage IV colorectal carcinoma)									
N	53			43		32	25	14	
$C_{\text{trough}}$	2.4 $\pm$ 2.9			56.7 $\pm$ 29.9		64.1 $\pm$ 29.3	85.4 $\pm$ 50.6	88.6 $\pm$ 30.4	
$C_{\text{peak}}$	227 $\pm$ 91			195 $\pm$ 66		201 $\pm$ 70	236 $\pm$ 109	213 $\pm$ 61	
IMCL CP02-0144 (Metastatic colorectal carcinoma)									
N	25			19		16			
$C_{\text{trough}}$	0			104.3 $\pm$ 56.2		120.6 $\pm$ 72.0			
$C_{\text{peak}}$	305 $\pm$ 112			310 $\pm$ 98		323 $\pm$ 126			
EMR 62 202-007 (Metastatic colorectal adenocarcinoma expressing EGFR and progressing on a defined Irinotecan based regimen)									
N	99	Monotherapy					65	34	
$C_{\text{trough}}$	1.7 $\pm$ 17.2						57.6 $\pm$ 27.2	ND	
$C_{\text{peak}}$	183 $\pm$ 44						ND	180 $\pm$ 49	
N	192	Concomitant Irinotecan					133	97	
$C_{\text{trough}}$	1.2 $\pm$ 14.3						64.1 $\pm$ 33.9	ND	
$C_{\text{peak}}$	193 $\pm$ 72						ND	182 $\pm$ 63	
IMCL CP02-9923 (Combination with chemotherapy in advanced colorectal carcinoma) (Course 1)									
N	119	4	5	57	5	2	2		
$C_{\text{trough}}$	3.2 $\pm$ 10.5	24.8 $\pm$ 23.2	15.6 $\pm$ 12.9	45.9 $\pm$ 35.2	92 $\pm$ 60	30.0 $\pm$ 26.9	28.5 $\pm$ 23.3		
(Course 2)									
N	10			41	3	2			
$C_{\text{trough}}$	32.5 $\pm$ 19.8			50.6 $\pm$ 34.4	48.0 $\pm$ 31.2	53.0 $\pm$ 49.5			
<b>Week</b>	<b>19</b>	<b>25</b>		<b>31</b>					
IMCL CP02-0141									
N	12	6		2					
$C_{\text{trough}}$	90.1 $\pm$ 39.0	99.0 $\pm$ 39.6		103 $\pm$ 4.2					
$C_{\text{peak}}$	267 $\pm$ 146	502 $\pm$ 600		196 $\pm$ 11.3					

**Table 3. Mean Cetuximab Serum Peak and Trough Concentrations at the Target Dose of 400mg/m<sup>2</sup>/250mg/m<sup>2</sup> in Other Trials (mean±SD)**

Week	1	2	3	4	5	6	7	8
IMCL CP02-9710 (Metastatic renal cell carcinoma)								
N	33	38	32	35	35	29	26	23
C <sub>trough</sub>	3.4±5.5	38.6±23.0	41.3±26.1	49.5±31.4	58.1±36.2	54.3±34.0	54.0±36.6	55.4±36.2
C <sub>peak</sub>	168±46	144±45	156±59	155±57	157±56	168±42	150±56	152±52
EMR 62 202-012 (D-D interaction, EGFr positive solid tumors)								
N	7	7	6	6				
C <sub>trough</sub>	0.3±0.6	35.2±10.6	47.8±16.1	52.2±20.7				
C <sub>peak</sub>	167±30	147±29	157±40					

Cetuximab concentration data were available from 25 patients in the ongoing trial CP02-0144. Comparisons of peak and trough concentrations among pilot, BB36 and Lonza manufacturing sites are shown in the following table:

**Table 4. Comparison of peak and trough concentrations among Pilot, BB36 and Lonza manufacturing sites (mean±SD)**

Manufacturing Site	Pilot	Lonza	BB36	GM Ratio	P
C <sub>peak</sub> (µg/ml)	172±47	205±74	312±110	1.52	0.0016
C <sub>trough</sub> (µg/ml)	55±37	60±30	112±64	1.26	>0.05

The geometric mean ratio between BB36 and Lonza associated pharmacokinetic values were 1.26 for the trough and 1.52 for the peak, and both failed to meet criteria for comparability. Therefore, we conclude that BB36 product is not pharmacokinetically comparable with the Lonza product.

Trial 0144 was planned to enroll 250 patients. In the present submission, efficacy and safety data from 111 patients were reported and among them 25 patients had peak and trough concentrations available. Although peak and trough concentrations were higher in Trial 0144 compared to other trials, the initial data showed the percentage of patients with severe skin rash similar among trials.

**Table 5. Severe Skin Rash Incidence by Trial**

Study Number	62 202-007	CP 02-9923	02-0141	02-0144	02-9710
#Patient treated	329	138	57	111	54
#Severe skin rash	47	20	7	10	7
Percentage	14.3%	14.4%	12.3%	9%	13%

### Summary

- The mean peak and trough concentrations in Trial CP 02-0144 in which the to-be-marketed drug material were used, were considerably higher than those in other trials.
- Two cases (Patient 019/1078 and Patient 600/0003) were reported of interstitial pneumonitis from Trial CP-0144, which were not found in other trials. But cetuximab concentrations were not determined for these two patients.
- No cetuximab concentrations were measured in 10 patients with severe skin rash in Trial CP 02-144. Among 25 patients with cetuximab concentration available in

this trial, 4 had  $C_{peak} > 500 \mu\text{g/ml}$ ; 5 had  $C_{peak} > 400 \mu\text{g/ml}$ ; 7 had  $C_{peak} > 300 \mu\text{g/ml}$ ; and 10 had  $C_{peak} > 200 \mu\text{g/ml}$ . No severe skin rash was reported in these 25 patients although cetuximab concentration considerably higher than those observed in other trials.

- In Trial CP 02-141, among 7 patients with severe skin rash, only 2 patients had cetuximab peak concentrations above  $300 \mu\text{g/ml}$ . According to the Clinical Safety Reviewer, the incidence of other adverse events was also similar among clinical trials.
- It appears that there is no direct relationship between extent of systemic drug exposure and skin rash.

### Conclusion

- Clinical and pharmacokinetic data support the approval of the product manufactured in Lonza facility.
- Since product manufactured in BB36 site is not pharmacokinetically comparable to the clinical trial product manufactured in Lonza facility, the sponsor is requested to submit the complete efficacy and safety results of Trial CP02-0144 as a supplement to support the marketing of the product manufactured in BB36 facility.

### Analytical

#### Cetuximab Concentration Determination

Three immunoassay methods (a Biacore assay (ImClone) and two ELISA (Merck KGaA and BMS)) have been used to determine the active moiety, cetuximab in serum. Within each study, only a single assay was used.

**Table 1. Assays Used in Clinical Trials**

Assay Method	Clinical Trials
Biacore (ImClone):	IMCL CP02-9923, IMCL CP02-0141, IMCL CP02-9710, IMCL CP02-0144
ELISA (Merck KGaA):	EMR 62 202-007, EMR 62 202-012

**Table 2. Standard Curve Fitting Equations and Range of Standard Curves**

Method	Curve Fitting Equation	Range of Standard Curve
BMS,	$Y = \text{max} + \frac{(\text{min} - \text{max})}{1 + (\text{conc}/\text{ED50})^B}$	_____
Merck KGaA	$y = a - d / [1 + (x/c)^b] + d$	_____
Biacore	$y = a - d / [1 + (x/c)^b] + d$	_____

At BMS, this model was used to describe the relationship between the OD readings and nominal concentrations of cetuximab standards on each plate. To ensure that measured concentrations fall within the limited standard curve range, each individual sample assayed at BMS was assayed at different dilutions. If two of the dilution samples fell within the standard curve range, the value reported was that which was closest to the mid-point of the curve.

At Merck KGaA, to ensure that measured concentrations fall within the limited standard curve range, each individual sample assayed at Merck KGaA was assayed at eight

different dilutions in run. For run — only — of those dilutions were selected which fitted best in the linear range of the standard curve. From these — dilutions, the value which was closest to the inflection point of the curve was reported.

At ImClone, this equation was used to describe the relationship between the SPR response units and nominal concentrations of cetuximab standards in each run. Clinical serum samples need to be diluted in assay buffer at a minimum dilution of — to reduce interference by human serum components. Cetuximab concentrations in nM were converted to µg/ml by multiplying by a factor of 0.1512 (MW=152,100 Dalton).

The correlation coefficient values ( $r^2$ ) for the standard curves from all runs were >0.997. In each plate, the deviations of the back-calculated concentrations from their nominal values were within ±15% (±20% from LLOQ) for at least three-fourths of the calibration standards.

### **Comparability of the Three Assays**

To evaluate the comparability of these three bioanalytical methods and facilitate comparison of clinical results across different studies, a three-way cross-validation using incurred samples was performed (Table 3). Comparability of the three assays was demonstrated as shown in Table 4.

**Table 3. Evaluation of Assay Performance**

Method	Intra-assay Precision (%CV)	Inter-assay Precision (%CV)	Accuracy (of the nominal value)	Concentration Range (µg/ml)
BMS	9.5%	2.0%	94-106%	
Merck KGaA	15%	7.5%	98-105%	
Biacore	15%	15%	85-115%	

To evaluate the comparability of these three bioanalytical methods and facilitate comparison of clinical results across different studies, a three-way cross-validation was performed. The results are shown in the following tables:

**Table 4. Comparison of the Accuracy and Precision of Three Immunoassays for Seven (A-G) Clinical Studies**

Tumor	Mean Concentration (µg/ml) with Pooled SD		
	BMS	ImClone	Merck KGaA
A	109.2 (6.6)	129.4 (24.4)	113.1 (8.7)
B	63.2 (4.0)	75.5 (9.4)	64.8 (7.4)
C	113.8 (11.3)	141.1 (14.6)	117.3 (7.6)
D	142.7 (6.8)	156.9 (11.2)	148.0 (23.9)
E	186.3 (17.5)	236.7 (27.6)	196.2 (13.1)
F	234.4 (26.0)	308.4 (48.8)	251.5 (11.3)
G	134.5 (12.5)	164.1 (8.0)	150.0 (13.8)
Overall	140.6 (14.0)	173.2 (24.6)	148.7 (13.4)
% Deviation from grand mean (154.1) with RSD (%)	-8.8% (10.0)	12.3% (14.2)	-3.5% (9.0)

### ***Summary***

- For each tumor type, the order of the means is always the same with ImClone showing the largest mean followed by Merck KGaA and then BMS.
- When compared by tumor, BMS and Merck KGaA were similar for all seven tumor types as well as overall. For tumor Types C, E and F, the ImClone mean is higher than either BMS or Merck KGaA.

### ***Conclusion***

The three assays for the determination of cetuximab in human serum have been validated to be sufficiently accurate, precise, linear and rugged for their intended purpose.

### ***Assays for Determination of Anti-Cetuximab Response***

In addition, two assays were used for the determination of anti-cetuximab responses. The assay used by ImClone to determine anti-cetuximab reactivity was a non-species-specific, double-antigen, radiometric assay specific for cetuximab. A sample was considered positive for an anti-cetuximab response if all the following 4 criteria were met:

- (a) A pretreatment baseline sample and at least 1 post-infusion sample were available for evaluation.
- (b) A sample had a post-baseline response greater than the upper limit of values observed in unexposed human serum (i.e., >10 ng/mL <sup>125</sup>I cetuximab binding).
- (c) The serum post-baseline value was  $\geq$ twice the baseline value.
- (d) Item c was satisfied for at least 2 consecutive determinations except if the positive determination was the final time point sampled.

In the Merck studies a sandwich ELISA was used to determine the anti-cetuximab responses. An anti-cetuximab response was considered positive if the mean optical density (OD) value of a serum sample was above the cut-off value of 0.100 OD and at least 3-fold the OD value of the respective pretreatment (screening) sample.

Both the ImClone and Merck assays are based on a similar principle that relies on capture and detection of anti-cetuximab antibodies by cetuximab itself. This detection scheme has been utilized for a variety of other therapeutic proteins and is state of the art. As these assays may be sensitive to the presence of excess amounts of free cetuximab in the clinical samples, anti-cetuximab responses should be interpreted with caution. In order to assess any potential interfering effects of free cetuximab, samples were monitored for both cetuximab and anti-cetuximab reactivity.

The observed incidence of anti-ERBITUX antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors, which might influence the incidence of anti-ERBITUX antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ERBITUX with the incidence of antibodies to other products may be misleading.