CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

CHEMISTRY REVIEW(S)

Review Cover Sheet

BLA STN 125084/0

ERBITUX (Cetuximab)

ImClone Systems Incorporated

Chana Fuchs, Ph.D. HFM-555
Wendy C. Weinberg, Ph.D. HFM-564
Division of Monoclonal Antibodies

CMC Review Data Sheet

1. **BLA#** STN# 125084/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 28-JAN-2004.

4. **REVIEWERS:** Chana Fuchs, Ph.D
Wendy C Weinberg, Ph.D.

5. **PREVIOUS DOCUMENTS[1]:**

Communications & Previous Documents	Document Date
CMC Pre-BLA Meeting	15-Aug-2003
Clinical Pre-BLA meeting	26-Apr-2001
CMC Pre-BLA Meeting	15-Feb-2001
Pre-supplement meeting	05-Oct-2001
Lonza biologics 483	13-Dec-2001
Filing Deficiency Letter	28-Oct-2001
Lonza Biologics 483	21-Nov-2003
ImClone Systems 483	14-Nov-2003
T-con	26-Nov-2003
T-con	09-Dec-2003
T-con	09-Dec-2003
T-con	09-Dec-2003
T-con	12-Dec-2003
T-con	15-Dec-2003
T-con	15-Dec-2003
T-con	16-Dec-2003
T-con	19-Dec-2003
T-con	22-Dec-2003
T-con	23-Dec-2003
T-con	23-Dec-2003
T-con	24-Dec-2003
T-con	29-Dec-2003
T-con	06-Jan-2004
T-con	09-Jan-2004
T-con	12-Jan-2004
T-con	14-Jan-2004
T-con	15-Jan-2004
T-con	16-Jan-2004
T-con	21-Jan-2004
T-con	21-Jan-2004
T-con	22-Jan-2004
T-con	23-Jan-2004
T-con	23-Jan-2004
T-con	26-Jan-2004
T-con	26-Jan-2004
T-con	27-Jan-2004

T-con	27-Jan-2004
T-con	27-Jan-2004
T-con	28-Jan-2004
T-con	29-Jan-2004
T-con	29-Jan-2004
T-con	29-Jan-2004
Lonza Biologics EIR	2001
Lonza Biologics EIR	2003
ImClone Systems EIR	2003

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original submission 125084/0	
Amendment 125084/0/003	05-Sep-2003
Amendment 125084/0/005	09-Oct-2003
Amendment 125084/0/006	12-Nov-2003
Amendment 125084/0/007	01-Dec-2003
Amendment 125084/0/011	24-Dec-2003
Amendment 125084/0/012	29-Dec-2003
Amendment 125084/0/013	16-Jan-2004
Amendment 125084/0/014	
Amendment 125084/0/015	

7. **NAME & ADDRESS OF APPLICANT:**

Name:	ImClone Systems Incorporated
Address:	33 Chubb Way
	Sommerville, NJ 08876
Representative:	Lily Lee, Ph.D. Vice President, Regulatory Affairs and Biostatistics
Telephone:	908-541-2250
Fax:	908-218-0555
Email:	Lily.Lee@imclone.com

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name:	Erbitux
b) Non-Proprietary Name:	cetuximab
c) Code name :	IMC-C225,BMS-564717,EMD-271786,C225,ch225
d) Common name:	anti-EGFR
e) Drug Review Status:	Fast Track
f) Chemical Type:	recombinant chimeric monoclonal antibody

9. **PHARMACOL. CATEGORY:** therapeutic monoclonal antibody to EGFR

10. **DOSAGE FORM:** Sterile parenteral solution.

11. **STRENGTH/POTENCY:**
(i) Concentration of Drug Product is 2 mg/mL in a 100mg/vial.

(ii) Potency is defined as:
(a) Percent inhibition relative to reference standard with a specification ratio of [redacted] using a proprietary cell based assay.
(b) binding relative to protein concentration measured using a proprietary ELISA and [redacted]

(iii) Dating period for vialed drug product is 36 months at 2-8°C.

12. **ROUTE OF ADMINISTRATION:** Intravenous Injection.

13. **ACID (Animal Component Information Database)**

Section 3.2.A.2.1.2 of the BLA and BLA review contain a description [redacted]

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY (Cytokine, MAb etc.),**

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

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	COMMENTS
				4	Adequate	Sufficient information was submitted to the BLA for review.
				3	Adequate	DMF-Active, last reviewed in 1987. BLA - Componant of Compendial material.
	I			2	Adequate	SOPs and validation reports for assays used were submitted to the BLA and reviewed by
				3	Adequate	
				2	Adequate	
	III			4	Adequate	
	III			4	Adequate	
	III			4, 3	Adequate	
				7	Adequate	
	V			4, 3	Adequate	All information re. facilities and process is in the BLA. A

			4	Adequate
			4	Adequate
	II		4	Adequate
	VI		4	Adequate

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA		

16. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Pending		
DMPQ - memo for CMC facilities review.	Approve	04-Feb-2004	Deborah Trout
DMPQ - closeout memo of Lonza Biologics PAI	approve		Deborah Trout
DMPQ - closeout memo of	approve		Deborah Trout
Immunogenicity assay validation	Post Marketing Commitment	28-Jan-2004	Anthony Mire-Sluis and Wendy Weinberg

Vial label and package review	Approve		Sharon Sickafuse Kristina Arnwine
DMETS trade name review	Approve	08-Jan-2004	Kristina Arnwine
DDMAC			Carole Broadnax
Environmental Assessment	Approve	08-Jan-2004	Marlene Swider, DMPQ

17. Inspectional Activities

A pre approval inspection (PAI) was conducted on 11/19 - 21/03 at Lonza Biologics, New Hampshire Facility for Cetuximab Drug Substance manufacture. This inspection is referred to in the CMC review and details are in the Establishment Inspection Report. This PAI was a follow-up to a PAI conducted at Lonza Biologics, New Hampshire Facility on 12/3 -14/01. Lonza Biologics has responded to the form 483 items for both inspections. Some commitments made by Lonza in their response to the 2001 483 were not fully implemented by the 2003 PAI (see 2003 form 483, item 1). Lonza's responses to the 2003 PAI 483 items were found appropriate, however, this should be followed up on the next inspection.

Note to future inspections:

[redacted]

A PAI was conducted on 12/1-5/03 at [redacted] facility for Cetuximab Drug Product manufacture by DMPQ. The sponsor has adequately responded to the form 483 items for this inspection.

A PAI was conducted on 11/4-14, 2003 at ImClone Systems Inc. BB36 facility. This PAI included the QC labs and final QA oversight for the Cetuximab drug substance produced at Lonza Biologics and Drug Product produced at [redacted]

APPEARS THIS WAY ON ORIGINAL

The CMC Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Cetuximab (Erbitux) was manufactured using a controlled and validated process. From a CMC perspective, Cetuximab manufactured at Lonza Biologics (Drug Substance) and [redacted] using the process and facilities described in the BLA, should be approved for the treatment of EGFR expressing metastatic colorectal carcinoma in combination with irinotecan in patients who are refractory to irinotecan based chemotherapy or as a single agent in patients who are intolerant to irinotecan-based chemotherapy.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Full validation of the ELISA and radiometric immunogenicity assays to determine accuracy, precision, sensitivity, specificity, and robustness of the assays used, and re-evaluate the available data or samples to establish the incidence of patient immune response to Cetuximab.

2. Drug Product stability data for the 36 months requested expiration dating.

3. Quantitative limits for Cetuximab carbohydrate composition when qualifying a new reference standard should be set prior to qualification of the next Cetuximab reference standard.

4. Biochemical assays that will be used in support of the release of Cetuximab reference standard should be qualified.

5. The following should be performed to further evaluate visible particulates in Cetuximab drug product:
   a. conduct studies showing the ability of the in- line filter to remove these particulates, deliver appropriate amount of drug to the patient, and not clog the filter. These studies should be conducted using representative lots of Cetuximab drug product at or beyond the 36 month expiration point as well as stressed lots for worst case analysis.
   b. Develop a quantitative assay to measure visible particulates in drug product. This assay will be required in support of any future changes in the formulation process.
   c. Initiate a kinetic stability study on visible particulate formation.

6. The following should be placed on real- time, long term stability study as outlined in ImClone's post approval stability protocol:
   a. One drug substance lot manufactured per year.
   b. One drug product lot manufactured per year.
   c. The first drug substance lot reprocessed at the [redacted]
   d. All drug substance lots reprocessed at the [redacted]

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- ERBITUX (Cetuximab) is supplied in a sterile, single-use, 50-mL vial containing 100 mg of Cetuximab at a concentration of 2mg/mL. Erbitux is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP. Each carton of Erbitux contains one vial.

- Expiry dating on Erbitux vials is 36 months from date of manufacture [redacted] months of stability data for the licensed manufacturing process, and additional supporting data from previous manufacturing processes has been submitted to the BLA in support of the 36 months expiration dating. Submission of 36 months stability data for the licensed manufacturing process is a post marketing commitment.

- Cetuximab is a chimeric mouse/human monoclonal antibody of the IgG1 subclass composed of [redacted] polypeptide chains: [redacted] heavy (γ) chains [redacted] light(κ) chains [redacted]

- [redacted]

- [redacted]

- The drug substance manufacturing process has been modified [redacted] during clinical development. Biochemical comparability study results between successive processes were submitted and reviewed under IND for appropriateness. These data are also included in the BLA. Drug product from each of the processes was used in clinical trials. Drug Products from [redacted] manufacturing processes [redacted] and the licensed Lonza [redacted] were used in the pivotal trial to support the safety and efficacy of Erbitux. Formulation of Cetuximab drug product has remained the same throughout the clinical trials.

- [redacted]

[redacted]

- A number of biochemical assays used in support of qualifying new reference standards, new working cell banks and extensive manufacturing changes have not been fully qualified. Performance of and data from these assays were assessed during the 2003 PAI at ImClone Systems. Full qualification of those assays is a post-marketing commitment.

- [redacted]

- Some assays or specifications used for lot release of Cetuximab drug substance and drug product were adjusted during the licensing process as described below. Lot release and stability data from drug substance and drug product lots released prior to specification changes have been re-evaluated and confirmed to meet the new specifications.
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- [redacted]

- Visible aggregates identified as Cetuximab in composition, are normally seen in drug product. [redacted] Filtration studies have shown that the visible aggregates are removed by the in line filter without significantly affecting the dose received by the patient or clogging the filter. [redacted] The expiration dating for Drug product is 36 months. ImClone has committed to perform additional filtration studies at potential worst-case scenario for visible aggregates as a PMC. Additionally, ImClone was asked to develop

a quantitative assay for visible aggregates to study the kinetics of aggregation and in support offuture changes in manufacturing.

- Immunogenicity to Erbitux was assessed using either a double antigen radiometric assay or an ELISA. The inadequate validation information regarding the assays' performance has limited the ability to assess clinical immunogenicity data appropriately. This is reflected in the Erbitux package insert. Additional validation of both assays for accuracy, precision, sensitivity, specificity and robustness is a post marketing commitment. Additionally, assessment of Erbitux immunogenicity using a validated assay is a clinical post-marketing commitment.

- The license application was originally submitted for 2 drug substance manufacturing processes, ImClone systems BB36 process – and Lonza Biologics process – Biochemical comparability of the two processes was submitted under IND as well as in the BLA. Additional PK comparability data requested during the IND and submitted to the BLA showed differences in PK that necessitated additional safety data to be collected and assessed for the BB36 process – material. Subsequently, BB36 process – was withdrawn from the BLA for future review in conjunction with the clinical PK data. The CMC section of the BLA was organized such that all information common to both the BB36 process and the Lonza process was submitted as part of the BB36 drug substance section, while the Lonza section contained only information that was unique to the Lonza process. Additionally, the BB36 drug substance section contains information relating to QC testing and lot release of drug substance and drug product. Every attempt was made to assure that the BLA review reflects the licensed Lonza process– exclusively, including any materials, cell banks, process, and product information that was incorporated into the BB36 section. Any details specific to the ImClone BB36 process– were removed.

- The Lonza biologics facilities and process for manufacturing Cetuximab drug substance was inspected during a PAI in December 2001. At that time it was assessed that Cetuximab was manufactured consistently, by a robust process, with appropriate precautions against contamination by cell substrate or adventitious agents. During a follow-up inspection at Lonza Biologics in November 2003, the consistency of Cetuximab manufacture from the time of the 2001 inspection through the last campaign prior to inspection was confirmed.

B. Description of How the Drug Product is Intended to be Used

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

- Premedication with an H_1 antagonist is recommended prior to administration of ERBITUX.

- ERBITUX should be administered through a low protein binding 0.22-micrometer in-line filter. 0.9% saline solution should be used to flush line at the end of infusion.

- Cetuximab drug product in the vial may have visible aggregates. ImClone has shown that the in-line filter can remove the aggregates normally experienced in an ERBITUX dose without a significant affect on the dosing and without blocking the in-line filter. Additional

testing of removal of potential worst-case levels of visible aggregates is a post-marketing commitment.

- Cetuximab should not be frozen. Preliminary studies have shown that visible aggregate formation increases if Cetuximab is stored between 0°C and -4°C.

- Cetuximab should not be diluted. A single dose requires the use of multiple vials of Cetuximab. For an average person of 70kg ($2m^2$) the initial loading dose of 800 mg will require the use of 8 vials of Cetuximab. 5 vials would be required for the weekly maintenance dose of 250 mg/m^2

- Vialed Cetuximab Drug Product has an expiration dating of 36 months at 2-8 °C. ImClone has shown that Cetuximab is stable for up to 12 hours at 2-8 °C and up to 8 hours at room temperature (20-25 °C) after transfer to infusion containers.

- Immunohistochemical evidence of positive EGFr expression using the DakoCytomation EGFr pharmDx™ test kit was a requirement for patient inclusion in the clinical trials. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized.

C. Basis for Approvability or Not-Approval Recommendation

- Erbitux was manufactured by a validated process with precautions against contamination by cell substrate or adventitious agents. Cetuximab manufactured by Lonza Biologics process — was manufactured consistently, leading to a safe and effective product, and should be approved.
- Post marketing commitments are described in the recommendation section above.

III. Administrative

A. Reviewers' Signature

Product Reviewer: Chana Fuchs, Ph.D. /S/ 2/10/04

Product Reviewer: Wendy C. Weinberg, Ph.D. /S/ 2/10/04

B. Endorsement Block

Product Branch chief: Patrick Swann, Ph.D. /S/ 2/10/04

Product Acting Division Director: Steven Kozlowski, M.D. /S/ 2/10/04

C. CC Block

Acting Office Director: Keith Webber, Ph.D.
Division of Monoclonal Antibodies File/BLA STN 125084/0

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