CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

Chemistry Review(s)

CMC Review Data Sheet

1. **BLA#** STN 125075/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 24-OCT-2003

4. **REVIEWER:** Steven Kozlowski, M.D.

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

Communications & Previous Documents	Document Date[2]
Pre-BLA Meeting	12-NOV-2002
Filing Review Letter Questions	03-MAR-2003
CMC Information Request	15-AUG-2003
CMC Questions	29-SEP-2003
T-com	08-MAY-2003
T-com	15-MAY-2003
T-com	05-JUN-2003
T-com	13-JUN-2003
T-com	07-OCT-2003

[1] Chronology of previous CMC communications between CDER and the firm and/or reviews
[2] Applicant's letter date or date of review and/or communication with applicant
[3] For OBP – IR letter or action letter

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

Submission(s) Reviewed	Document Date
STN 125075/0 Original Submission	27-DEC-2003
STN 125075/0.011 Response to Filling Quest	25-MAR-2003
STN 125075/0.023 Labeling	19-MAY-2003
STN 125075/0.025 Stability Update	06-JUN-2003
STN 125075/0.038 Efficacy in Ab Positive Pt	04-AUG-2003
STN 125075/0.035 PAI 483 Responses	15-AUG-2003
STN 125075/0.041 Resp to CMC IR	29-AUG-2003
STN 125075/0.042 Stability Update	02-SEP-2003
STN 125075/0.043 Resp to CMC IR	02-SEP-2003
STN 125075/0.044 Resp to CMC IR	12-SEP-2003
STN 125075/0.049 Resp to CMC IR	03-OCT-2003
STN 125075/0.050 Resp to CMC IR	07-OCT-2003
STN 125075/0.051 Resp to 9/29/03 Quest	10-OCT-2003
STN 125075/0.055 Resp to 9/29/03 Quest	21-OCT-2003

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

Name:	Genentech, Inc.
Address:	1 DNA Way
	South San Francisco, CA
Representative:	Robert L. Garnick, Ph.D.
Telephone:	650-225-1202

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

a) Proprietary Name:	Raptiva
b) Non-Proprietary Name (USAN):	efalizumab
c) Code names:	G176CR
d) Common name	anti-CD11a
e) Drug Review Status:	Standard
f) Chemical Type:	recombinant humanized monoclonal antibody

9. **PHARMACOL. CATEGORY:** therapeutic monoclonal antibody to CD11a

10. **DOSAGE FORM:** lyophilized powder for injection

11. **STRENGTH/POTENCY:**
(i) Concentration of reconstituted product 100 mg/mL
(ii) Potency is defined as ——— using a proprietary cell adhesion inhibition assay
(iii) Dating period is 24 months when lyophilized, 8 hours post-reconstitution.

12. **ROUTE OF ADMINISTRATION:** subcutaneous injection

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

Table 1 in Section 3.2.S.2.3.1 lists starting materials of biological origin. These materials and their countries of origin are listed below:

*

*

*

*

*

* The Raw Material, ——— Prior to ——— the

The Marketing Authorization for the ——— is available upon request. This was reviewed on the PAI 6/16-27/03

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY (Cytokine, MAb etc.), MAIN SPECIES MOLECULAR WEIGHT (can be a range), HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S (or say Non-glycosylated):** Efalizumab is a full length, IgG1 kappa isotype antibody composed

with a total molecular weight of approximately 150,000 daltons.

Figure 1

Figure 2

15. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	4	N/A		meets USP/Ph. Eur. standards
—	II	—	—	1	Adequate	21-OCT-1999	
—	II	—	—	1	Adequate	See consult	CDRH

[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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	6809	Initial efalizumab development at Xoma for Psoriasis
IND	—	—
IND	—	—
IND	—	—

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics			
Establishment Status			
Pharm/Tox/Biopharm			
Labeling Nomenclature Committee	Approve	10/9/03	Charlie Hoppes
Methods Validation*			
OPDRA#	Approve	10/9/03	Charlie Hoppes
Environmental Assessment	Approve	10/27/03	under DMPQ review
DMPQ	Approve	10/27/03	Carol Rehkopf
Other: (CDRH/CBER)	Approve	10/7/03	Viola Hibbard

* Methods may be sent to CDER labs for verification for NDA submissions

Review trade name for medical error avoidance

17. **Inspectional Activities**

A pre approval inspection was conducted on 6/16-27/03 at the Genentech South San Francisco Facility. This inspection is referred to in the CMC review and details are in the Establishment Inspection Report. The sponsor has responded to the form 483 items.

Notes for future inspections:

a. —

b. —

c.

d. —

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Raptiva (efalizumab) is manufactured using a well-controlled and validated process. From a CMC perspective, Raptiva should be approved for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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

1) The sponsor will commit to

2) The first full scale lot protocol should be placed on full stability.
3) As part of the safety post-marketing clinical study, patients who develop inflammatory or other significant AE, such as arthritis, should be assessed for antibody responses to efalizumab at an appropriate interval post cessation of Raptiva. In addition any patient who shows an early response to Raptiva that is not sustained during therapy should also be assessed for antibody responses to efalizumab at an appropriate interval post cessation of Raptiva. [See clinical PMCs]
4) Develop an assay that can detect Raptiva neutralization by antibody responses to efalizumab and archive relevant samples for this assay. [See clinical PMCs]

II. Summary of Chemistry Assessments

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

- A Raptiva vial contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochoride monohydrate, 4.3 mg of L-histidine and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 mL after reconsitution. Lot release assays suggest the drug product and drug substance are manufactured consistently.
- The drug substance, efalizumab, is a humanized IgG kappa monoclonal antibody isotype antibody Efalizumab binds with high affinity to CD11a, the a-subunit of lymphocyte function-associated antigen-1 (LFA-1), a ß2 integrin, and leads to LFA-1 down modulation. Efalizumab blocks the binding of LFA-1 to its ligand, intercellular adhesion molecule 1 (ICAM-1) and inhibits T-lymphocyte-mediated activation and functions such as migration. T-lymphocyte activation and migration play a role in the keratinocyte proliferation of Psoriasis. Efalizumab can also bind other leukocytes and its effects on lymphocytes are not

specific, thus it is immunosuppressive. Efalizumab does not lead to lymphocyte destruction through antibody effector functions.

- Efalizumab is produced in [redacted] process at [redacted] using a [redacted] Chinese hamster ovary (CHO) [redacted] cell line. The efalizumab in [redacted] included in the process. The first lot [redacted] should be placed on stability [See Section 3.2.S.2.5 CMC IR question 25 follow up and I.B.(2) above]
- The manufacturing process for efalizumab includes [redacted] and [redacted]. The viral clearance studies have used a [redacted] These have been validated by [redacted] Some additional data has been requested for one of the [redacted] to confirm the [redacted]. [See Section 3.2.A.2 CMC IR question 57 follow up].
- Although [redacted] used in the manufacture of Raptiva, [redacted] acceptance criteria help prevent product contamination. The sponsor uses [redacted] This is acceptable. Sponsors using [redacted] changing to alternative sources of [redacted] and this has been discussed with this sponsor regarding this product (pre-BLA meeting 12-NOV-02) and other of their products [redacted]
- Over the course of development, drug substance manufacturing was moved from XOMA to Genentech. This was associated with changes in [redacted] [BLA Section 3.2.S.2.6]. The changes led to some differences in product [redacted] and presence of [redacted] The formulation [redacted] was also changed [redacted] The product pharmacokinetics were altered with the manufacturing change. Similar pharmacodynamics, safety and efficacy in phase III studies allowed the experience with both manufactured products to be combined in support of this application.
- Investigation of the observed pharmacokinetic differences by Genentech did not implicate [redacted] or formulation [redacted] as the primary cause. Although no data directly demonstrated [redacted] pharmacokinetics, the specification for a [redacted] of efalizumab was modified to increase control of product [redacted] [STN 125075/0.021].
- Raptiva [redacted] was validated with [redacted] however they were not done at full capacity. Since manufacturing will be primarily performed at full capacity and a full load places more [redacted] additional full load data was provided and the sponsor committed to performing an additional [redacted] full load validation studies distributed between the [redacted] used in manufacturing. [See DMPQ review and I.B.(1) above]

Redacted 108

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information

- The sponsor suggested broad acceptance criteria for a number of stability indicating and general assays. These were narrowed to better reflect Genentech's manufacturing experience and will be reassessed after [redacted] are manufactured.
- The immunogenicity assay may not be as sensitive as it could be since there may be residual serum levels of Raptiva at the time immunogenicity was evaluated ([redacted]) that can interfere with the assay. Data provided by the sponsor suggest that even in the worst case, the sensitivity of the assay at [redacted] post last dose is equivalent to [redacted] ng/mL. This could be improved but is acceptable. Even though the clinical data suggest antibody positive patients responded as well as antibody negative patients, development of an assay to measure neutralizing antibody would be of value. This could be used to evaluate high titer samples from prior clinical studies and in post marketing studies. Development of an assay to assess neutralizing antibody should be a post marketing commitment. [See Section 5.3.1.4 CMC IR question 60 follow up and I.B.(3,4) above]

B. Description of Drug Product and how it is Intended to be Used

- Raptiva (efalizumab) for injection is provided in single-use stoppered vials as a lyophilized powder for reconstitution with 1.3 mL sterile water for injection (non-USP due to a broader pH range) provided in a pre-filled syringes. Each Raptiva vial contains 150 mg of efalizumab to deliver 125 mg in 1.25 mL. Raptiva is used at 1 mg/kg/week subcutaneously, after a first dose of 0.7 mg/kg, for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The lyophilized drug product has an expiration dating of 24 months at 2-8°C and can be used for 8 hours post reconstitution at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

- Raptiva is manufactured by a robust process [redacted] Raptiva is manufactured consistently, leads to a safe and effective product,.and should be approved.
- Post marketing commitments are described in the recommendation section above.

III. Administrative

A. Dr. Steven Kozlowski M.D., Acting Deputy, Division of Monoclonal Antibodies, Lab Chief LIB/DMA/OBP/OPS/CDER [redacted] 10/24/03

B. Dr. Keith Webber Ph.D., Director, Division of Monoclonal Antibodies, OBP/OPS/CDER [redacted] 10/24/03