CENTER FOR DRUG EVALUATION AND RESEARCH

BLA APPLICATION NUMBER:

125156

CHEMISTRY REVIEW(S)

Review Cover Sheet

BLA STN 125156/0

LUCENTIS (Ranibizumab)

Genentech, Inc.

Michelle Frazier-Jessen, Ph.D. HFD-123
Joseph Kutza, Ph.D. HFD-123
Division of Monoclonal Antibodies

CMC Review Data Sheet

1. **BLA#** STN 125156/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 27-JUN-2006

4. **REVIEWERS:** Michelle Frazier-Jessen, Ph.D.
Joseph Kutza, Ph.D.

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

Previous Documents	Document Date[2]
Clinical Pre-BLA Meeting	21-SEP-2005
CMC Pre-BLA Meeting	09-NOV-2005
Filing Review (45 days)/Deficiency Com.	13-FEB-2006
T-com	24-FEB-2006
T-com	04-MAY-2006
T-com	10-MAY-2006
T-com	17-MAY-2006
T-com	09-JUN-2006
T-com	14-JUN-2006
T-com	16-JUN-2006
E-com	24-APR-2006
E-com	04-MAY-2006
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E-com	27-MAY-2006
E-com	31-APR-2006
E-com	01-JUN-2006
E-com	02-JUN-2006
E-com	05-JUN-2006
E-com	06-JUN-2006
E-com	13-JUN-2006
E-com	15-JUN-2006
E-com	16-JUN-2006
E-com	23-JUN-2006

[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

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

Submission(s) Reviewed	Document Date
STN 125156/0 Original Submission	29-DEC-2005
STN 125156/0.004 Resp to CMC IR	21-FEB-2006
STN 125156/0.005 Resp to CMC IR	24-FEB-2006
STN 125156/0.007 Resp to CMC IR	23-MAR-2006
STN 125156/0.009 Stability Update	10-APR-2006
STN 125156/0.013 Resp to CMC IR	25-MAY-2006
STN 125156/0.014 Resp to CMC IR	25-MAY-2006
STN 125156/0.015 Stability Update	21-MAY-2006
STN 125156/0.017 Resp to CMC IR	31-MAY-2006
STN 125156/0.018 Stability Update, PMCs	01-JUN-2006
STN 125156/0.019 PMCs	02-JUN-2006
STN 125156/0.020 Labeling	05-JUN-2006
STN 125156/0.021 Stability Update	06-JUN-2006
STN 125156/0.022 Labeling	09-JUN-2006
STN 125156/0.023 Labeling	13-JUN-2006
STN 125156/0.024 Resp to CMC IR	16-JUN-2006
STN 125156/0.025 PMCs	23-JUN-2006
STN 125156/0.026 Resp to TFRB IR	26-JUN-2006

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: Lucentis
b) Non-Proprietary Name: ranibizumab
c) Code name: rhuFab V2
d) Common name: Recombinant humanized anti-VEGF monoclonal antibody fragment
RFB002
rhuFab VEGF (V2)
rhuFab VEGF (AMD)
rhuFab VEGF (2nd Generation)
anti-VEGF Fab
AMD rhuFab
e) Drug Review Status: Priority Review
f) Chemical Type: Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (C)

9. **PHARMACOL. CATEGORY:** Therapeutic monoclonal antibody Fab fragment to vascular endothelial growth factor (VEGF).

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

11. **STRENGTH/POTENCY:**
(i) The concentration of Lucentis (ranibizumab) Drug Substance and Drug Product is 10 mg/ml.
(ii) Potency is defined as [redacted]
(iii) Dating period for vialed drug product is 18 months when stored at 2°C -8°C.

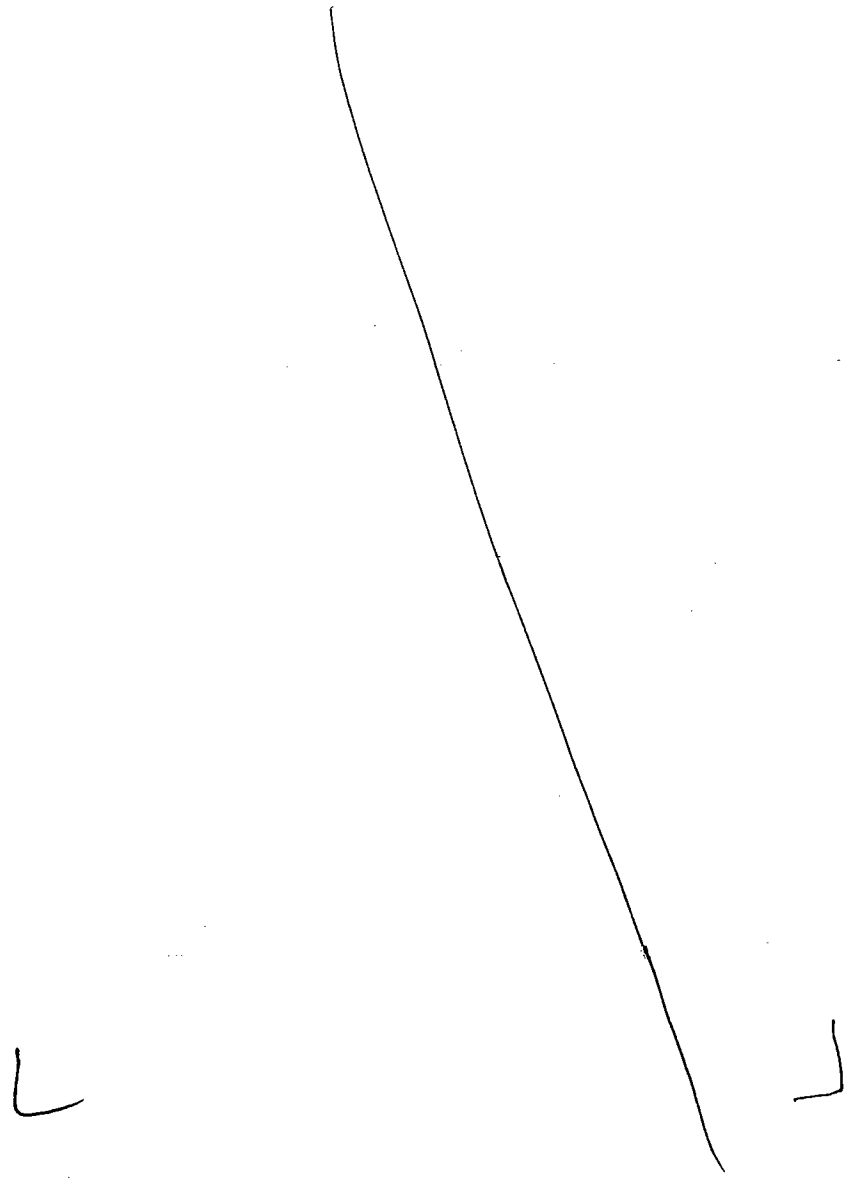
12. **ROUTE OF ADMINISTRATION:** Intravitreal injection of 0.5 mg

13. **ANIMAL-DERIVED RAW MATERIALS:**

[redacted]

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**
Ranibizumab is an IgG1 kappa isotype Fab moiety of a recombinant humanized monoclonal antibody rhuMAb VEGF.

[redacted]



15. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III		—	1	Adequate	10-JUL-2003	Meets USP requirements

—	III	—	Type I Glass Vials	4	N/A	N/A	Meets USP/Ph. Eur.standards

[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
[redacted]	[redacted]	[redacted]

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
Establishment Status	Approve	16-JUN-2006	Shirnette Ferguson
Labeling Nomenclature Committee/Office of Drug Safety	Approve	26-JUN-2006	DMETS
OPDRA[#]	Approve	26-JUN-2006	DMETS
Environmental Assessment	Approve	12-JUN-2006	Patricia Hughes [TFRB]
TFRB	Approve	27-JUN-2006	Patricia Hughes Michelle Clark-Stuart

[#] Review trade name for medical error avoidance

17. **INSPECTIONAL ACTIVITIES:**

The pre-approval inspection (PAI) for Lucentis DS was performed at the Genentech South San Francisco facility from 07-MAR-2006 to 09-MAR-2006 .

[redacted]

During a telecon between the FDA ranibizumab CMC reviewers and the sponsor on 10-MAY-2006, Genentech provided a follow-up statement to the issue of [redacted] that was deemed adequate for purposes of the BLA review process. However, the finding will be forwarded to Team Biologics for follow-up during their next biennial inspection, currently scheduled for Fall 2006.

The PAI for Lucentis [redacted] was waived on 27-JUN-2006. This waiver was based on the criteria as required per [redacted]. The review committee recommended that the inspection be waived due to the following reasons:

(1) [redacted]

(2) [redacted]

These reasons justified waiving the inspection. Lucentis DP batch records will be reviewed during the next biennial inspection.

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of ranibizumab (Lucentis™) is well controlled, and leads to a product that is pure and potent. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

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

The sponsor has agreed to the following post-marketing commitments:

1. Develop and validate assays to detect and characterize immune response to ranibizumab:
   A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.
   B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies [See Clinical PMCs].

   The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment ; — The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes [See Clinical PMCs].

   Date of submission of protocol and statistical analysis plan: February 28, 2007.
   Date of submission of final study report: September — 2008.
   The need for an additional clinical study will be determined based on the results from the analysis described above.

3. To revise release specifications, shelf-life specifications and in-process limits for ranibizumab drug substance and drug product after — commercial manufacturing runs to reflect increased manufacturing experience. These revisions to the Quality control system, the corresponding data from the — commercial manufacturing runs and the analysis plan used to create the revisions will be submitted as ——— by or before June 30, 2008.

4. To perform additional Lucentis stability studies at 40°C using Ion Exchange Chromatography (IEC) to demonstrate that the corrective actions taken at [— —] to address the atypical accelerated stability profile observed in the Lucentis 2005 qualification campaign have been sufficient.
   Specifically:

- A one time stability study consisting of — Lucentis Drug Product launch lots are placed at 40°C and tested by IEC at [redacted] months.
- These — Lucentis Drug Product lots are derived from the following:
  - — of these Lucentis Drug Product lots are manufactured from distinct lots of [redacted]
  - At least — of these [redacted] lots are aliquoted and used to manufacture two Lucentis Drug Product lots.

Data will be submitted as a —— by or before March 31, 2007.

II. Summary of Chemistry Assessments

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

- [redacted]

  A Lucentis vial contains — of — ranibizumab in — histidine HCl, —% w/v trehalose dihydrate, and —% w/v polysorbate 20, pH 5.5 and is designed to deliver — of ranibizumab in — of sterile liquid solution, respectively. Lot release assays suggest the drug product and drug substance are manufactured consistently.

- The drug substance, ranibizumab, is a humanized IgG_1, kappa monoclonal Fab fragment.

- [redacted]

- [redacted]

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry 172

- The sponsor suggested broad acceptance criteria for release specifications, shelf-life specifications and in-process limits for ranibizumab Drug Substance and Drug Product and proposed to revise these specifications after manufacturing runs to reflect increase manufacturing experience. This proposal was formalized as a post-marketing commitment [See PMC item # 3].

- Three assays were developed for assessment of anti-ranibizumab antibodies in human serum. The first assay developed for detection of anti-ranibizumab antibodies was a direct ELISA that was used in the Phase I and some Phase II studies. This assay was not sensitive enough to detect potential low titer responses, and had other issues as well. A subsequent assay using an ECLA bridging format was developed with greatly improved sensitivity. Confirmation of a positive response was by immunodepletion. This assay was capable of detecting both IgM and IgG antibodies to ranibizumab. However, this assay had a fairly high false positive rate, as was demonstrated in the initial results that were obtained. Therefore, another confirmatory assay, a direct ECLA was developed in order to distinguish "true" anti-ranibizumab responses; confirmed positive responses are then titered. This assay is also fairly sensitive; however, the format of this assay is such that only IgG-mediated anti-ranibizumab antibodies are detected. The clinical immunogenicity data provided from these assays suggest that a percentage of patients develop IgG anti-ranibizumab antibodies and that a percentage of these patients have inflammatory episodes. The sponsor did not adequately characterize the anti-ranibizumab response with regards to safety and efficacy. A post-marketing commitment is recommended to develop validated, sensitive and accurate assays to further characterize immune responses (binding antibodies) to Ranibizumab with regards to immunoglobulin isotype (IgM and IgG isotypes) of immune responses to ranibizumab and to determine if anti-ranibizumab antibodies are neutralizing [See PMC items 1 and 2].

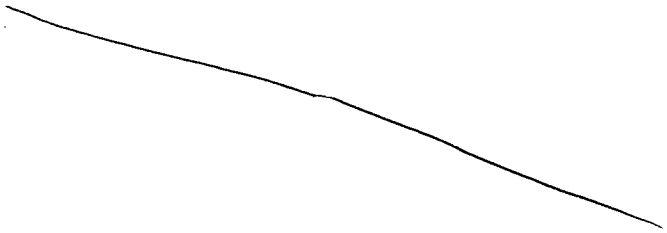
B. Description of How the Drug Product is Intended to be Used

- Lucentis is indicated for d in patients with neovascular (wet) age-related macular degeneration.

- Lucentis (ranibizumab) Drug Product is provided as a single use vial in a nominal of ranibizumab per vial (10 mg/ml).

- Lucentis is administered by intravitreal injection in total volume of 0.05 ml (0.5 mg). Lucentis is recommended to be administered once a month. After the first 4 monthly doses, treatment may be continued monthly or reduced to one injection every 3 months.

- Lucentis vials should be refrigerated at 2°C-8°C and protected from direct sunlight. Lucentis vials should not be shaken or frozen. The recommended expiration dating period for Lucentis Drug Product is 18 months under these storage conditions. Genentech proposes a drug substance expiration date of [redacted] and a drug product expiration date of [redacted] based on [redacted] of real time data from the [redacted] qualification lots, [redacted]



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C. Basis for Approvability or Not-Approval Recommendation

- Lucentis is manufactured by a [redacted] process with precautions for contamination [redacted] Lucentis is manufactured consistently, leads to a safe and effective product, and should be approved for the proposed indication.

- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

III. Administrative

A. Reviewers' Signature

Product Reviewer: Michelle Frazier-Jessen , Ph.D.

Product Reviewer: Joseph Kutza, Ph.D.

B. Endorsement Block

Product Branch chief: Patrick Swann, Ph.D.

Product Acting Division Director: Kathleen Clouse, Ph.D.

C. CC Block

Acting Office Director: Steven Kozlowski, M.D.
Division of Monoclonal Antibodies File/BLA STN 125156/0

108 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry 2 of 2