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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN-125085/0

Chemistry Review(s)

Review Cover Sheet

BLA STN 125085/0

AVASTIN (Bevacizumab)

Genentech, Inc

Michelle Frazier-Jessen, Ph.D. HFM-555

Joseph Kutza, Ph.D. HFM-555

Division of Monoclonal Antibodies

CMC Review Data Sheet

1. **BLA#** STN 125085/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** 22-FEB-2004
4. **REVIEWERS:** Michelle Frazier-Jessen, Ph.D.
Joseph Kutza, Ph.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS¹:**

| <u>Previous Documents</u> | <u>Document Date²</u> |
|---|----------------------------------|
| Clinical Pre-BLA Meeting | 27-JUN-2003 |
| CMC Pre-BLA Meeting | 24-JUL-2003 |
| Filing Review (45 days)/Deficiency Com. | 28-NOV-2003 |
| T-com | 20-OCT-2003 |
| T-com | 23-OCT-2003 |
| T-com | 30-OCT-2003 |
| T-com | 6-NOV-2003 |
| T-com | 13-NOV-2003 |
| T-com | 17-NOV-2004 |
| T-com | 20-NOV-2003 |
| T-com | 11-DEC-2003 |
| T-com | 18-DEC-2003 |
| T-com | 22-DEC-2003 |
| T-com | 12-JAN-2004 |
| E-com | 13-JAN-2004 |
| E-com | 21-JAN-2004 |
| T-com | 21-JAN-2004 |
| E-coms (3) | 22-JAN-2004 |
| T-com | 22-JAN-2004 |

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:**

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-----------------------------------|----------------------|
| STN 125085/0 Original Submission | 26-SEP-2003 |
| STN 125085/0.004 Resp to CMC IR | 20-NOV-2003 |
| STN 125085/0.011 Resp to CMC IR | 18-DEC-2003 |
| STN 125085/0.013 Resp to CMC IR | 23-DEC-2003 |
| STN 125085/0.014 Stability Update | 23-DEC-2003 |
| STN 125085/0.023 Resp to CMC IR | 23-JAN-2004 |
| STN 125085/0.026 PMCs | 30-JAN-2004 |
| STN 125085/0.030 PMCs | 12-FEB-2004 |
| STN 125085/0.031 PMCs | 13-FEB-2004 |

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STN 125085/0.032 PMCs
STN 125085/0.033 PMCs, Stability

17-FEB-2004
20-FEB-2004

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: Avastin
- b) Non-Proprietary Name: bevacizumab
- c) Code name: G180CL, G180CU, G180DL (Drug Product)
- d) Common name: anti-human recombinant VEGF
- e) Drug Review Status: Fast Track
- f) Chemical Type: recombinant humanized monoclonal antibody

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

10. DOSAGE FORM: Sterile parenteral solution.

11. STRENGTH/POTENCY:

- (i) The concentration of Avastin (bevacizumab) Drug Substance and Drug Product is 25 mg/ml.
- (ii)
- (iii) Dating period for vialled product is 18 months when stored at 2°C -8°C, 8 hours post-dilution.

12. ROUTE OF ADMINISTRATION: Intravenous infusion in 100 ml of 0.9% Sodium Chloride for Injection, USP

13. ACID (Animal Component Information Database)

Raw Material:

Vendor:

Source:

Adventitious Agent Control:

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Raw Material:

Vendor:

Source:

Adventitious Agent Control:

Raw Material:

Vendor:

Source:

Adventitious Agent Control:

Raw Material:

Vendor:

Source:

Adventitious Agent Control:

14. PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:

Bevacizumab is a IgG1 isotype monoclonal antibody

L

J

The molecular weight of intact bevacizumab is 149,199 daltons for the antibody form.

The mature bevacizumab protein is expressed in a recombinant CHO cell line. are shown below.

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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 | - | - | 4 | N/A | | Meets USP/Ph. Eur. standards |
| - | III | - | - | 3 | Adequate | 2000 | |
| - | III | - | - | 1 | Adequate | 12-FEB-2003 | |

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 |
|----------|--------------------|--|
| BB IND | 7023 | Initial bevacizumab development at Genentech |

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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 | 20-FEB-2004 | Colleen Hoyt |
| Labeling Nomenclature Committee | Approve | 27-JAN-2004 | Linda Kim-Jung [DMETS] |
| OPDRA [#] | Approve | 27-JAN-2004 | Linda Kim-Jung |
| Environmental Assessment | Approve | 18-FEB-2004 | Carolyn Renshaw [DMPQ] |
| DMPQ | Approve | 18-FEB-2004 | Carolyn Renshaw |

[#] Review trade name for medical error avoidance

17. **Inspectional Activities**

The pre-approval inspection (PAI) for Avastin at the Genentech South San Francisco facility was waived on 14-JAN-2004 . This waiver was based on the criteria as required per SOPP 8410, "Determining When Pre-licensing/pre-approval Inspections(PLI/PAI) are Necessary." The review committee recommended that the inspection be waived due to the following reasons:

- (1) The best utilization of CDER resources at this time indicated an inspection was not warranted. Information was available from a pre-license inspection performed from 6/16-27/03 at the South San Francisco facility for Raptiva, a similar monoclonal antibody. A FDA Form 483 was issued at the close of the inspection and responses to the 483 were reviewed and deemed adequate by the inspectors.
- (2) Genentech provided their inspection history and a comparison of the Avastin process to their other antibody processes that outlined the similarities of Avastin production to three of Genentech's licensed products, Raptiva, Rituxan, and Xolair. Avastin only uses _____ Similar _____ were covered by previous inspections.

These reasons justified waiving the inspection. Avastin batch records _____

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 bevacizumab (Avastin™) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. 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. To develop a validated, highly sensitive and accurate assay for the detection of an immune response (binding antibodies) to Bevacizumab. The assay method should include procedures for accurate detection of antibodies to Bevacizumab in the presence of serum containing Bevacizumab and vascular endothelial growth factor. [See Clinical PMCs]
2. To more accurately characterize the immune response to Bevacizumab in one or more clinical trials using the more sensitive, validated assay described above. The proposal for collection of these data must obtain samples at adequate time points, both early and late in treatment. [See Clinical PMCs]
3. To revise release and shelf-life specifications for drug substance and drug product based upon tolerance intervals on a yearly basis to reflect increased manufacturing experience. The methods of analysis should be sufficiently clear to permit independent calculation of the results provided.
4. To perform *in vitro* and *in vivo* viral and adventitious agent testing per ICH Q5A on a future full scale cGMP batch of Bevacizumab at _____ to support the _____ proposed limit of *in vitro* cell age per ICH Q5A.
5. To perform genetic stability testing per ICH Q5B on a future full scale cGMP batch of Bevacizumab at _____ to support the _____ proposed limit of *in vitro* cell age.

II. Summary of Chemistry Assessments

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

- An Avastin vial contains 25 mg/ml bevacizumab in _____ sodium phosphate, pH 6.2, _____ trehalose dihydrate, and _____ polysorbate 20 and is designed to deliver either 100 mg or 400 mg of bevacizumab in 4 ml or 16 ml of sterile liquid solution, respectively. Lot release assays suggest the drug product and drug substance are manufactured consistently.

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- Bevacizumab has
Bevacizumab degradation is dramatically increased with exposure to temperatures above 2-8°C. These degradation pathways are
and active, respectively, in the potency assay. The observed in bevacizumab was unique with respect to the high levels initially observed. Extensive characterization studies indicate that the observed are composed of both slow and fast-dissociating components. The fast-dissociating components are sensitive to protein concentration and pH (i.e., reversible), whereas the slow-dissociating components are not (irreversible). These attributes are controlled for within the lot release criteria by examining both diluted and neat samples via
- The potency of bevacizumab is measured utilizing a bioassay that quantifies the ability of bevacizumab to inhibit
Bevacizumab inhibits the mitogenic activity of rhVEGF by preventing VEGF from binding to endothelial cells. The assay is stability indicating, as it can detect changes in activity in bevacizumab samples exposed to elevated temperature, intense light, and basic pH. However, the assay sensitivity has an RSD of 5-6% that is reflected in the reporting scheme (two significant digits). Furthermore, although the potency assay is an important stability-indicating assay, it is not capable of picking up the degree of subtle degradation that the assays are capable of (i.e., degradation will not be observed in the potency assay until the data display substantial degradation). Taking this information into account, as well as the relative potencies observed in the lots manufactured and used in the clinic to date, it is strongly recommended that potency acceptance criteria not be widened beyond
- The sponsor suggested broad acceptance criteria for a number of stability indicating and general assays, based upon the use of Tolerance Intervals and other additional criteria, such as assay variability. These were narrowed to better reflect Genentech's manufacturing experience and will be re-assessed after are manufactured, as part of a post-marketing commitment [See PMC item # 3].
- Evaluation of the current assay utilized to detect potential human anti-bevacizumab antibodies (i.e., immunogenicity) revealed numerous problems. The current assay has a sensitivity of only Serum concentrations above as well as the presence of study drug (bevacizumab) in the serum interfered with the assay sensitivity. Furthermore, samples for the assay were taken at time points when considerable study drug was on board (2 weeks after administration; less than one half-life), that interfered with the ability to accurately detect the presence of anti-bevacizumab antibodies. The sponsor was aware of the Agency's concerns prior to the BLA submission and chose not to improve the current assay prior to submission of the BLA. Instead, the sponsor committed to developing and validating a more sensitive assay post-licensure. The sponsor plans to utilize this assay in a future clinical trial involving patients treated with bevacizumab alone (versus the current

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- The drug substance, bevacizumab, is a humanized — monoclonal antibody isotype antibody. — Bevacizumab binds with high affinity to Vascular Endothelial Growth Factor (VEGF), and prevents the ability of VEGF to interact with its receptors, Flt-1 and KDR, on endothelial cells. Characterization data suggest that bevacizumab's mechanism of action is mediated via steric hindrance. Studies utilizing in vitro models of angiogenesis have shown that the interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation, functions important for both normal and pathologic vasculogenesis (i.e., tumors). Administration of bevacizumab to xenotransplant models of cancer in nude (athymic) mice resulted in decreased microvascular growth and inhibition of metastatic disease progression. Although bevacizumab can bind to Fc receptors and the complement receptor, it does not appear to mediate its effects through antibody dependent cellular cytotoxicity or complement dependent cytotoxicity.
- Bevacizumab is produced in a — cell culture process at the — scale, using a suspension-adapted Chinese hamster ovary (CHO) transfectant cell line.
- The sponsor utilizes a — scale culture system to develop and validate critical cell culture process parameters in combination with the — full scale manufacturing process. It was noted during the course of the review that the sponsor had utilized numerous — scale batches to support the proposed — limit of in vitro cell age for the current Master Cell Bank. Furthermore, genetic stability testing was performed on material from a — scale batch at approximately —. In contrast, manufacturing experience with the — full scale process was only out to —. There were several concerns with the proposed limit of in vitro cell age utilizing data from the — system. ICH Q1A guidance defines a Pilot scale batch as a "batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch." A significant difference in viability between — scale batches was observed. Furthermore, the — scale batches were not operated under cGMP (e.g. QA/QC review). Therefore, it is not clear that, despite this characterization, the — scale is fully representative of the — scale. Subsequent to the original submission, the sponsor has generated numerous full scale batches beyond — with the longest time point at —. It was felt that data from the — culture was sufficient to support the proposed — limit. The sponsor was asked and agreed to perform the appropriate testing on this batch to meet the requirements for adventitious agent testing and genetic stability, per ICH Q5A and Q5B. However, the complete data will not be available prior to the decision date for the file. It was felt that the most appropriate way to deal with this issue was via a post-marketing commitment whereby the sponsor will submit the data to the file upon completion. [See PMCs 4 and 5]

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regimen which is bevacizumab in combination with 5-FU-based chemotherapy). Samples of these patients will be collected at later time points in order to minimize the role of study drug on board.

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

- Avastin, used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon and rectum. The recommended dose of Avastin is 5 mg/kg given once every 14 days as an IV infusion until disease progression is detected.
- Avastin (bevacizumab) Drug Product is currently provided as single use vials in two configurations: Nominal 100 mg of bevacizumab per vial (4 ml of 25 mg/kg) and nominal 400 mg of bevacizumab per vial (16 ml of 25 mg/kg). However, the 400 mg configuration and will be maintained on the stability protocol in order to support the proposed expiry dating of all vial configurations.
- Avastin is diluted in a total volume of 100 ml of 0.9% Sodium Chloride for Injection, USP, for intravenous infusion. Avastin infusions should not be administered or mixed with dextrose solutions. Diluted Avastin solutions for infusion may be stored at 2°C-8°C for up to 8 hours.
- Avastin vials should be refrigerated at 2°C-8°C and protected from direct sunlight. Avastin vials should not be shaken or frozen. The recommended expiration dating period for Avastin Drug Product is 18 months under these storage conditions. The sponsor initially asked for an expiry of _____ but did not have complete data at the time of submission to support this time point. As Avastin Drug Product is susceptible to substantial degradation under accelerated conditions, ICH Q1E guidance states that extrapolation of expiry dating is not recommended. The sponsor plans to submit the additional data to support the _____ dating period when it becomes available to increase the expiry dating.
- Avastin was originally proposed to be shipped at ambient temperatures. However, the stability profiles for Avastin demonstrated dramatic degradation in one of the key stability-indicating assays (_____) at ambient temperature. These degradation products included _____ (that could be potentially immunogenic). As the sponsor originally planned to ship Avastin Drug product at ambient temperatures, shipping data was not originally supplied for 2-8°C. However, all material used in clinical trials was shipped at 2-8°C, and data was provided showing the degradation that occurs when stored at ambient temperatures. Information was also provided for product that was exposed to temperature excursions to simulate what may happen during shipping at ambient temperatures. The degradation profiles were characterized, but of unknown clinical significance. Because of these reasons and the fact that the degradation was completely avoidable

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by shipping at 2-8°C, the sponsor was informed that Avastin Drug Product should be shipped at 2-8°C. The sponsor agreed to this change. [See 125085/0.023].

C. Basis for Approvability or Not-Approval Recommendation

- Avastin is manufactured by a robust process with precautions for contamination by _____ Avastin 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.

APPEARS THIS WAY
ON ORIGINAL

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III. Administrative

A. Reviewers' Signature

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

/S/

02-24-04

Product Reviewer: Joseph Kutza, Ph.D.

/S/

02-24-04

B. Endorsement Block

Product Branch chief: Patrick Swann, Ph.D.

/S/

02-24-04

Product Acting Division Director: Steven Kozlowski, M.D.

/S/

02-24-04

C. CC Block

Acting Office Director: Keith Webber, Ph.D.

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