CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN-125085/0

Administrative

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

DATE: February 26, 2004 /S/

FROM: Sharon Sickafuse
Regulatory Project Manager
Division of Review Management and Policy, HFM-588
Office of Drug Evaluation VI

TO: STN 125085/0

SUBJECT: SBA Equivalent for
Bevacizumab
Genentech, Incorporated
U.S. license number 1048

Indications and Usage
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.

Dosage Form, Route of Administration, and Recommended Dosage
AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile liquid for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and — Water for Injection, USP, pH 6.2. The 400 mg product is formulated in 960 mg □,□-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and — Water for Injection, USP, pH 6.2.

The recommended dose of AVASTIN is 5 mg/kg given once every 14 days as an IV infusion until disease progression is detected.

AVASTIN therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of AVASTIN.

Basis for Approval

The following reviews, filed in the CDER correspondence section of the license file for STN 125085/0 comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
CMC	Michelle Jessen, Ph.D.	2-24-04
	Joseph Kutza, Ph.D.	
Clinical (Safety and Efficacy)	Ellen Maher, M.D.	2-26-04
Non-clinical Pharm/Tox	Anita O'Connor, Ph.D.	2-25-04
	Barbara Wilxcox, Ph.D.	2-25-04
Clinical Pharmacology	Iftekhar Mahmood, Ph.D.	1-14-04
Biostatistical	Bo Zhen, Ph.D.	2-23-04
Bioresearch Monitoring	Jose Tavarez-Pagan	1-30-04
Facilities	Carolyn Renshaw	2-19-04

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Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 22, 2003
Final revision 2/18/04 (incorporates Michael Smedley's comments)

From: Carolyn Renshaw, facility reviewer, TFRB/DMPQ/OC/CDER, HFD-328

Applicant Genentech, Inc.

Subject: STN 125085/0
First line of treatment of metastatic colorectal cancer in combination with 5-fluorouracil based chemotherapy

Product: Bevacizumab (Avastin)

To: File for STN 125085/0
Michelle Jessen, Ph.D, HFM-564, OPS/OBP/DMA, BLA CMC Reviewer
Joseph Kutza, Ph.D., OPS/OBP/DMA, BLA CMC Reviewer, HFM-555
Sharon Sickafuse, OND/ODEVI/DRMP, HFM-588
Ellen V. Maher, MD, OND/ODEVI/DTBOP, HFM-573
Patricia Keegan, MD, OND/ODEVI/DTBOP, HFM-570

Through: Michael D. Smedley, Acting Branch Chief, HFD-328, TFRB/DMPQ/OC

/S/ 2/18/04

Submission Date: 9/26/03
FDA received Date: 9/30/03
Action Due Date: 3/31/04

Review Recommendation: I recommend approval with post marketing commitments as described in the conclusion section of this memo.

Sections Reviewed:

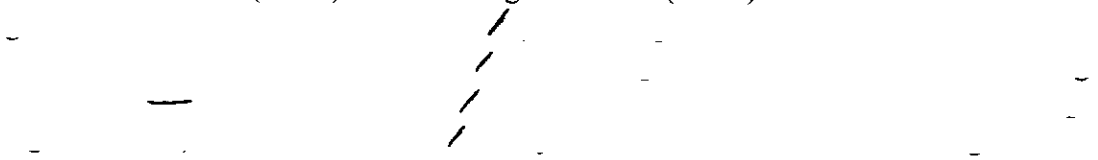
Module 2: Overall Summary
Module 3: Quality
Drug Substance
3.2.S.1 Manufacturer
3.2.S.2.2 Description of Manufacturing Process and Controls
3.2.S.2.3 Control of Materials (FYI only)
3.2.S.2.4 Controls of Critical Steps and Intermediates

3.2.S.2.5	Process Validation and/or Evaluation (review for consistency only)
3.2.S.6	Container Closure System
Drug Product	
3.2.P.1	Description and Composition of the Drug Product (FYI)
3.2.P.4	Control of Excipients (FYI)
3.2.P.5	Control of Drug Product (FYI)
3.2.P.7	Container Closure System
Appendix	
3.2.A.1	Facilities and Equipment
Amendments	
#011	Responses to deficiency letter questions 7-20 Submission date – 12/17/03
#023	Categorical Exclusion Request Submission date – 1/23/04
#031	Responses to 2/12/04 telecon Submission date – 2/13/04

Summary:

AVASTIN (Bevacizumab) is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralizing the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth. AVASTIN. (Bevacizumab) in combination with 5-fluorouracil based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon and rectum.

Bevacizumab is produced in a — process at the — scale, using a — Chinese hamster ovary (CHO) cell line. The source of cells is either the Master Cell Bank (MCB) or a Working Cell Bank (WCB) derived from the MCB.



The following figures depict the process —

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Figure 2

Bevacizumab Drug Substance and Drug Product are manufactured at the Genentech licensed multi-product facilities in South San Francisco. Genentech states these facilities are operated in cGMP compliance, with standard operating procedures (SOPs) in place to describe all procedures and controls. A compliance check will be performed prior to approval. Validated procedures ensure that products and are effectively removed.

operations are performed on the processing and other equipment used to produce bevacizumab. Environmental monitoring of air pressure, viable and nonviable particulates, and surface bioburden are performed; are documented and evaluated.

To prevent cross-contamination,

cell line.

The effectiveness of procedures is evaluated prior to introduction of a new product per an approved comparability protocol.

Review Comments

BLA Item 15: Establishment Description

- Genentech, Inc. (License No. 1048) is responsible for the manufacture, testing, and release of bevacizumab Drug Substance (Bulk for Storage) and Drug Product. All operations in the manufacture of bevacizumab Drug Substance and Drug Product occur at:

    - Genentech, Inc
      1 DNA Way
      South San Francisco, CA 94080-4990
      U.S. License No. 1048

3.2.A.1 Facilities and Equipment

- The facilities for bevacizumab are multiproduct utilizing both concurrent and campaigned manufacturing schedules.
- The production of bevacizumab Drug Substance — — located on the Genentech South San Francisco (SSF) Campus. The production of Bevacizumab Drug Product occurs in the Genentech Parenteral Manufacturing Facility (GPMF).
- The following table describes multi-use areas that are campaigned — — and used concurrently — —).

APPEARS THIS WAY
ON ORIGINAL

Table 1

[redacted]

- Genentech states that concurrent manufacturing is controlled through [redacted] I need more information regarding control of concurrent manufacturing:
  - [redacted]
  - [redacted]

(For Genentech's response, please refer to the last section of this memo regarding my review of Genentech's response to Question 7 of Amendment 125085/0.011.)

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