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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: January 26, 2004

FROM: Patricia Keegan, M.D., /S/   /S/
             Division Director
             Division of Biological Therapeutic Oncology Products

SUBJECT: Recommendation for Approval Action on BLA STN 125085 for
             AVASTIN, in combination with intravenous 5-fluourouracil-based
             chemotherapy regimens, for the initial treatment of metastatic colorectal
             cancer.

TO: STN 125085

Introduction

Bevacizumab (AVASTIN™) is the first anti-angiogenic agent to be approved for the
treatment of cancer. Approval for the initial treatment of colorectal cancer is based on
the highly significant results in a large, multicenter trial demonstrating 30% improvement
in survival (from 15.6 to 20.3 months), as well as significantly improved progression-free
survival, higher response rate, and more durable responses. Bevacizumab is a
recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic
activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay
systems. Bevacizumab contains human framework regions and the
complementarity-determining regions of a murine antibody that binds to VEGF.
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1
and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors
leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models
of angiogenesis. Both anti-neoplastic activity (anti-tumor effect) and toxicities are
thought to be mediated through the same mechanism of action (inhibition of endothelial
cell proliferation and new vessel formation) in tumors and as well as in normal tissues.

Regulatory History

Genentech submitted the original IND application for bevacizumab (BB-IND 7023) on
January 31, 1997. Eleven studies have been conducted under this IND. The clinical
development program included Phase 2 and 3 trials of bevacizumab in combination with
chemotherapy for the treatment of metastatic colorectal cancer, metastatic breast cancer,
and advanced non-small cell lung cancer.

A discussion of the pivotal development plan for bevacizumab in the treatment of metastatic colorectal cancer was held in January of 1999. The design of the major efficacy study (Genentech Protocol 2107g) was discussed with FDA on March 7, 2000. Preliminary evidence of activity was available from a randomized, active-controlled, dose-ranging study of 5-FU and leucovorin alone or in combination with one of two doses of bevacizumab (Protocol 780g), however shortly after the completion of that study, the results of a randomized trial comparing treatment with 5FU and leucovorin against the bolus-IFL regimeñ (irinotecan, 5FU, and leucovorin, also referred to as the "Saltz regimen") became available, which demonstrated convincing evidence of superior survival with bolus-IFL over 5FU and leucovorin.

Based upon these data, the bolus-IFL regimen became the new standard of care for initial treatment of metastatic colorectal cancer, replacing the previous 5FU/leucovorin regimens. The consequences of this shift were discussed with Genentech and the control arm of the proposed study was changed to the bolus-IFL regimen. FDA noted that there were no data on toxicity profile and tolerability of the combination of bevacizumab with bolus-IFL. As an alternative to conducting additional Phase 1 and 2 studies of bevacizumab in combination with bolus-IFL, Genentech proposed to conduct a three-arm, active-controlled study of bolus-IFL (Arm 1), bolus-IFL with bevacizumab (Arm 2), and 5FU, leucovorin plus bevacizumab (Arm 3). Based on a planned interim analysis after 100 patients had been enrolled in each of the three arms, one of the two bevacizumab -containing arms would be dropped from the study. In the event of unacceptable toxicity, enrollment into Arm 2 would be discontinued, whereas in the event of that the toxicity profile was deemed acceptable, enrollment into Arm 3 would be discontinued. The primary efficacy comparison would be conducted between Arm 1 and the remaining bevacizumab arm that continued accrual (Arm 2 or 3).

Following interim safety review, the toxicity profile of Arm 2 was deemed reasonably safe and enrollment into Arm 3 was terminated after 110 patients had been enrolled.

CLINICAL STUDIES
(See reviews by Virginia Ellen Maher, M.D. and Boguang Zhen, Ph.D.)

<u>Efficacy</u>
A single, large, multicenter trial provided the primary efficacy data submitted in support of this application. Protocol 2107g was a randomized, placebo-controlled, multicenter study of chemotherapy with or without bevacizumab in the first-line treatment of 925 patients with metastatic colorectal cancer. The primary endpoint of this trial was improvement in overall survival, with secondary efficacy endpoints of progression-free survival, overall response rate, and response duration.

Supportive data were obtained in Protocol 780g, a randomized, multi-center, open-label, active-control, dose-ranging study of 5-fluourouracil\leucovorin alone or in combination with bevacizumab in 104 patients.

2

In addition, the interim results of an ongoing National Cancer Institute (NCI)-funded cooperative group study (E3200) were submitted to an IND held by the NCI, with a letter permitting FDA (but not Genentech) access to the data in support of the marketing application for bevacizumab. The E3200 study provided data regarding the activity of single agent bevacizumab in the initial treatment of colorectal cancer as well as supporting safety information for the combination of bevacizumab and the FOLFOX4 chemotherapy regimen.

Study AVF2107g

· Study AVF 2107g was a randomized, placebo-controlled, three-arm study assessing the safety and effectiveness of bevacizumab in combination with chemotherapy for the initial (first-line) treatment of metastatic colorectal cancer. As described above, there was a planned interim assessment of safety of the two bevacizumab-containing arms (Arms 2 and 3, below), with the intent of discontinuing enrollment in one of these two arms. The primary and secondary efficacy comparisons were conducted in the two arms reaching full accrual, while safety was assessed in all patients. The three treatment arms for the study were:

- Arm 1: bolus-IFL (irinotecan 125 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV, and leucovorin 20 mg/m^2 IV given once weekly for 4 weeks every 6 weeks) plus placebo

- Arm 2: bolus-IFL (irinotecan 125 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV, and leucovorin 20 mg/m^2 IV given once weekly for 4 weeks every 6 weeks) plus bevacizumab 5 mg/kg IV infusion every 2 weeks

- Arm 3: 5FU/LV (5-fluorouracil 500 mg/m^2 IV and leucovorin 20 mg/m^2 IV given weekly for the first 4 weeks of a 6- week cycle) plus bevacizumab 5 mg/kg IV infusion every 2 weeks

Data from 2 patients enrolled at a single site (t̲   ˥) are excluded from all analyses of safety and efficacy [refer to Mr. Tavarez-Pagan's review], thus efficacy data are based on 923 patients registered and randomized. A total of 813 patients were randomized to bolus-IFL plus placebo (Arm 1; n=411) or bolus-IFL plus bevacizumab (Arm 2; n=402). Among the 813 patients randomized to Arms 1 and 2, the median age was 60 years, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients. The baseline entry characteristics were similar across the study arms.

Efficacy analyses were conducted in the intent-to-treat population in the two major study arms and are presented in Table 1 and Figure 1, on the following page.

3

Table 1
Study AVF 2107g Efficacy Results

	IFL + Placebo	IFL + BEVACIZUMAB 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-Free Survival[a]		
Median (months)	6.4	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

[a] $p < 0.001$ by stratified logrank test.

[b] $p < 0.01$ by χ^2 test.

The survival analyses are presented with error bars demonstrating that for all later landmark times (12, 18, and 24 months) the differences in survival are significantly different.

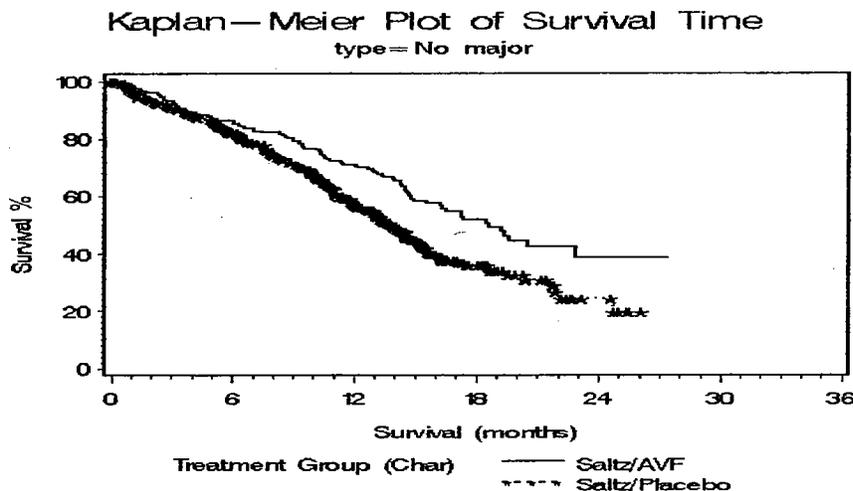### Duration of Survival All Patients in AVF 2107g
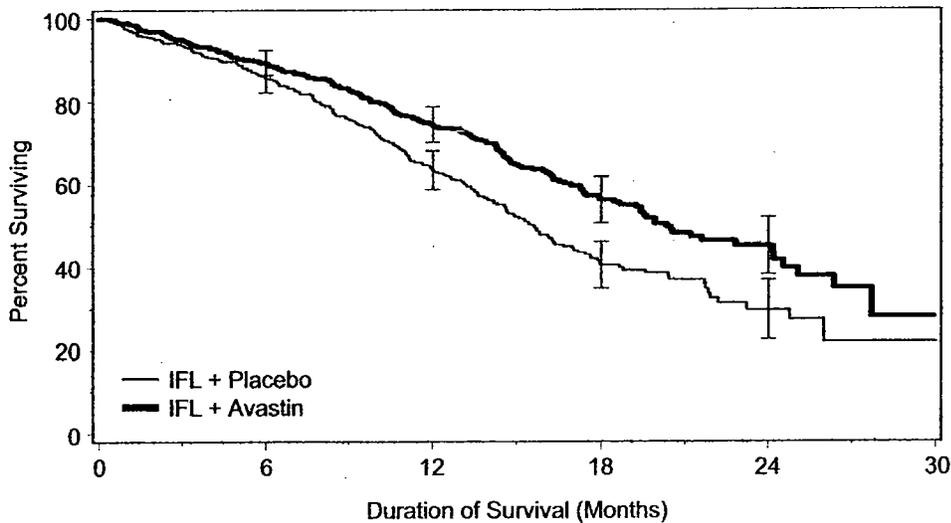
Error bars represent 95% confidence intervals.

4

<u>DSI review (See review by Jose Tavarez-Pagan)</u>

During the course of the Protocol 2107g, FDA became aware of a study conduct issues at two study sites; this resulted in two directed inspections. Warning letters were issued for both sites and the data from one site \[C   ] were excluded from all analyses, while data from the other site \[   ] were excluded from the secondary efficacy analyses due to concerns regarding the quality of the data. An additional issue arising during the conduct of the trial was pharmacy errors, resulting in the dispensing of the wrong study drug product, i.e., placebo rather than bevacizumab or bevacizumab rather than placebo. This occurred at several sites, however no patient received more than one dose of the incorrect drug product. Modifications were made to the packaging of the masked study drug product, which appeared to resolve this problem.

In addition, clinical sites inspections conducted during the course of the BLA review and review of case report forms and other records identified numerous deviations from the clinical protocol. The range of issues was wide, including deviations from protocol eligibility, failure to administer treatment as prescribed, failure to collect protocol-specified laboratory information needed to assess safety. These issues were categorized as major violations [e.g., enrollment of patients with pancreatic cancer (n=2) or without evidence of metastatic disease (n=1)] and minor violations. Overall, major protocol violations were identified in 38% of patients in the IFL plus placebo and 47% of patients in the IFL plus bevacizumab arm.

In an attempt to explore the effect of protocol violations, a sensitivity analysis for survival was conducted in which all patients with major protocol violations were excluded (shown below). This analysis yielded similar results to that observed in the ITT analysis with highly statistically significant results (p<0.01). Even in an additional sensitivity analysis in which all patients with major or minor protocol violations were excluded, a similar improvement in survival was observed that was also statistically significant (p<0.03)

Kaplan—Meier Plot of Survival Time
type = No major

Treatment Group (Char) ——— Saltz/AVF
▼▼▼▼ Saltz/Placebo

5

The efficacy results are robust, however the results of statistical tests comparing the results of the two study arms will be affected by inclusion or exclusion of subjects with protocol violations. Therefore, p values cited in labeling and advertising should be reported as approximations, rather than as specific values.

Study AVF780g

Study AVF0780g, was a randomized, open-label, multicenter study conducted in 104 patients with newly diagnosed metastatic colorectal cancer. The three treatment arms were:

- 5-Fluorouracil and Leucovorin (5-fluorouracil 500 mg/m^2, leucovorin 500 mg/m^2 weekly for 6 weeks every 8 weeks) [n=36]
- 5-Fluorouracil and Leucovorin plus Bevacizumab 5 mg/kg every 2 wks [n=35]
- 5-Fluororuacil and Leucovorin plus Bevacizumab 10 mg/kg every 2 wks [n=33]

The co-primary endpoints in this trial were overall response rate and progression-free survival. Overall survival was a secondary endpoint. The results of this trial are presented in the following table.

Table 2

Study AVF 780g Efficacy Results

	5-FU/LV	5-FU/LV + BEVACIZUMAB 5 mg/kg	5-FU/LV + BEVACIZUMAB 10 mg/kg
Number of Patients	36	35	33
Overall Survival			
Median (months)	13.6	17.7	15.2
Progression-Free Survival			
Median (months)	5.2	9.0	7.2
Overall Response Rate			
Rate (percent)	17	40	24

The analysis plan for the trial did not adjust for multiple endpoints. Using a simple Bonferroni adjustment for multiple endpoints and multiple comparisons, only the improvement in progression-free survival between the 5 mg/kg arm and the control arm was statistically significant (p=0.005, unadjusted/ p=0.0125 adjusted). However, the observed efficacy outcomes are improved for all measured in the bevacizumab arms as compared to chemotherapy alone. On inspection, the magnitude of

6

improvement was consistently highest in the 5 mg/kg bevacizumab arm and this dose/schedule was selected for confirmation of efficacy in Study AVF2107g.

Study E3200
The Eastern Cooperative Oncology Group (ECOG) is conducting a large, randomized, open-label, three-arm trial in patients with colorectal cancer who have progressed following a 5-fluorouracil and irinotecan-based chemotherapy. Patients were randomized to bevacizumab alone, bevacizumab in combination with the FOLFOX4 regimen (5-fluorouracil, leucovorin, and oxaliplatin), or FOLFOX4 alone. The Data Safety Monitoring committee for the study, based on routine surveillance, recommended closure to accrual to the bevacizumab alone arm based on inferior survival in that arm as compared to patients randomized to FOLFOX4. Based on the incomplete and unaudited data provided under an IND submission, follow-up information is currently available for 143 patients with 45 deaths in the bevacizumab arm and for 138 patients with 25 deaths in the FOLFOX arm. The median survival times were 191 days for patients who received bevacizumab alone vs. 335 days for those treated with FOLFOX (p =0.012, log-rank test). The result implies that patients treated with single-agent bevacizumab may have inferior survival as compared with patients treated with the FOLFOX regimen of 5-fluorouracil, leucovorin and oxaliplatin. However, the results should be interpreted with caution since the data were incomplete and unaudited.

Safety
The safety profile of bevacizumab was assessed in the 923 patients enrolled in protocol 2107g, 104 patients enrolled in Study AVF 780g, and in an integrated safety (ISS) database containing 1032 patients who received bevacizumab across all clinical studies. The ISS database includes patients from the bevacizumab-containing arms of 2107g and 780g but not the control group patients.

Safety was also reviewed in select studies conducted under BB-IND 7921 (held by NCI) and in the NCI AdEERs database of expedited reports.

With regard to the analysis of safety, both deviations from planned treatment and failure to rigorously collect safety information/laboratory data have lead to difficulties in fully characterizing adverse events. Genentech has agreed to collect additional data to further characterize the incidence and clinical course of the following Bevacizumab-induced adverse events: hypertension, proteinuria, gastrointestinal perforation and/or impaired wound healing.

The most serious adverse events associated with bevacizumab were gastrointestinal perforation and impaired wound healing, life-threatening and fatal hemorrhage, hypertensive encephalopathy, serious and life-threatening thromboembolic events, nephrotic syndrome, and congestive heart failure. Additional information on these events is summarized below.

The most common severe (NCI-CTC Grade 3–4) adverse events among 1032 patients receiving bevacizumab in Genentech-sponsored studies were asthenia, pain, hypertension, diarrhea, and leukopenia.

The most common adverse events of any severity among the 742 patients, for whom data on all toxicities regardless of severity were recorded, receiving bevacizumab in Genentech-sponsored studies were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

Serious Adverse Events

- Gastrointestinal Perforation and Abnormal Wound Healing: Gastrointestinal perforation and wound dehiscence, complicated by intra-abdominal abscesses, occurred at an increased incidence in patients receiving bevacizumab as compared to controls in randomized trials of colorectal cancer. The incidence of gastrointestinal perforation was 2% in patients receiving bevacizumab in combination bolus ILF chemotherapy. Of note, bevacizumab has also been shown to impair wound healing in pre-clinical animal models. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. These events have generally required surgical intervention; despite this, some events were fatal. The current package insert contains a Boxed Warning regarding these events, noting that bevacizumab should not be initiated within 28 days following major surgery or until the surgical incision is fully healed, whichever occurs later. The package insert also recommends caution in the timing of elective surgery following completion of bevacizumab, taking into account the long half-life of the drug.

- Hemorrhage: Two distinct patterns of bleeding have occurred in patients receiving bevacizumab. The first is minor hemorrhage, most commonly Grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events. The highest rate of serious hemorrhagic events occurred in a randomized study in patients with non–small cell lung cancer receiving chemotherapy with or without bevacizumab, In this study, four of 13 (31%) bevacizumab-treated patients with squamous cell histology and two of 53 (4%) bevacizumab-treated patients with non-squamous histology experienced life-threatening or fatal pulmonary hemorrhage as compared to none of the 32 (0%) patients receiving chemotherapy alone. Additional serious hemorrhagic events reported in clinical studies were gastrointestinal hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, and hemorrhage within a CNS metastasis.

Because the incidence of thromboembolic events is increased in patients receiving bevacizumab, assessment of the safety of administration of anti-coagulants with bevacizumab was conducted. In Study AVF 2107g, 53 of 392 (14%) patients who received bolus-IFL plus bevacizumab and 30 of 396 (8%) patients who received bolus-IFL plus placebo had a thromboembolic event and received full-dose warfarin. Two patients in each treatment arm (four total) developed bleeding complications; for

8

the two events in the IFL plus bevacizumab arm, both patients had marked elevations in their INR at the time of the event.

- Hypertensive encephalopathy and hypertensive crisis: Across all clinical studies, development or worsening of hypertension resulted in hospitalization or discontinuation of bevacizumab in 17/1032 patients. Four of these 17 patients developed hypertensive encephalopathy. Severe hypertension was complicated by subarachnoid hemorrhage in one patient.

The incidence of hypertension and severe hypertension was increased in patients receiving bevacizumab in Study AVF 2107g (see Table 3). The NCI CTC grading scale defines grade 3 hypertensive adverse events as those requiring medical management, a criterion that covers relatively modest as well as very dramatic increases in hypertension. In an attempt to provide clarity, FDA conducted an analysis in which the incidence of hypertension (systolic and/or diastolic) using various cut-points was assessed. The following table presents incidence of hypertension by two of these cut-points as a function of treatment arm in Study AVF 2107g. Among patients with severe hypertension in the bevacizumab arms, slightly over half the patients (51%) had a diastolic reading greater than 110 associated with a systolic reading less than 200.

Table 3
Incidence of Hypertension and Severe Hypertension in Study 1

	Arm 1 IFL+Placebo (n=394)	Arm 2 IFL+BEVACIZU MAB (n=392)	Arm 3 5-FU/LV+BEVACIZ UMAB (n=109)
Hypertension[a] (>150/100 mmHg)	43%	60%	67%
Severe Hypertension[a] (>200/110 mmHg)	2%	7%	10%

[a] This includes patients with either a systolic or diastolic reading greater than the cutoff value on one or more occasions.

- Thromboembolic Events: In Study AVF 2107g, 18% of patients receiving bolus-IFL plus bevacizumab and 15% of patients receiving bolus-IFL plus placebo experienced a Grade 3 or 4 thromboembolic event. The incidence of the following Grade 3 and 4 thromboembolic events were higher in patients receiving bolus-IFL plus bevacizumab as compared to patients receiving bolus-IFL plus placebo: cerebrovascular events (4 vs. 0 patients), myocardial infarction (6 vs. 3), deep venous thrombosis (34 vs. 19), and intra-abdominal thrombosis (13 vs. 5). The sole exception was the incidence of pulmonary embolism, which was higher in patients receiving bolus-IFL plus placebo (16 vs. 20).

In Study AVF 2107g, 53 of 392 (14%) patients who received bolus-IFL plus bevacizumab and 30 of 396 (8%) patients who received bolus-IFL plus placebo had a

thromboembolic event and received full-dose warfarin. Eleven of 53 (21%) patients receiving bolus-IFL plus bevacizumab and one of 30 (3%) patients receiving bolus-IFL developed an additional thromboembolic event.

- Nephrotic Syndrome: Nephrotic syndrome occurred in five of 1032 (0.5%) patients receiving bevacizumab in Genentech-sponsored studies. One patient died and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of bevacizumab. No patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of bevacizumab. The incidence of proteinuria (urine dipstick value $\geq$ 1+ on urinalysis) is increased in patients receiving bevacizumab in placebo-controlled trials. The incidence and severity of proteinuria appears to be dose-related. In addition, the risks of proteinuria may be increased in patients with renal carcinoma who have undergone nephrectomy and in patients receiving concurrent palmidronate.

- Congestive Heart Failure Congestive: NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 22 of 1032 (2%) patients receiving bevacizumab in Genentech-sponsored studies. Congestive heart failure occurred in six of 44 (14%) patients receiving bevacizumab and concurrent anthracyclines. Congestive heart failure occurred in 13 of 299 (4%) patients who received prior anthracyclines and/or left chest wall irradiation. In a controlled study, the incidence was higher in patients receiving bevacizumab plus chemotherapy as compared to patients receiving chemotherapy alone.

Given the nature of the product (protein), immune responses were anticipated and patients enrolled in the phase 3 studies were assessed for evidence of immune responses. However, the assay used was insensitive and the timing of sample collection was such that the reliability of the results, due to interference with assay results caused by the presence of bevacizumab in serum samples was uncertain. The applicant agreed to develop sensitive assays for the detection of binding and neutralizing antibodies and to collect data in future studies to better characterize the immune response to bevacizumab.

Clinical Pharmacology
See Dr. Iftekar Mahmood's review

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The half-life for bevacizumab) is longer than other products in this class (humanized antibody) and insufficient late sampling was obtained to characterize the terminal half- life of bevacizumab when administered in the indicated population.

Because certain toxicities, notably hypertension and impaired wound healing, seem to occur and persist throughout treatment, it is important to characterize the elimination half-life of bevacizumab as it may relate to reduction in the risk of toxicity (impaired wound healing) and resolution of hypertension. It is projected, based on a half-life of 20 days, that bevacizumab will be present in patients, at pharmacologically active doses, for several months after termination of dosing. The applicant will further characterize the pharmacokinetic profile after termination of dosing under an agreed upon post-marketing commitment.

The clearance of bevacizumab varies by body weight, by gender, and by tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. However, in Study AVF 2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with bevacizumab as compared to females and patients with low tumor burden. Because the relationship between bevacizumab pharmacokinetics, include exposure, and clinical outcomes has not been explored, extrapolations regarding effective doses and schedules of bevacizumab should not be made on the basis of comparable exposure.

Pharmacology/Toxicology
(See reviews by Anita O'Connor and Barbara Wilcox)

Pharmacokinetic studies were conducted in nude (athymic) mice, rats, rabbits, and cynomolgus monkeys. Cynomulgus monkere were the most relevant species based relative affinity of bevacizumab for primate VEGF and pharmacologic activity (bevacizumab does not have high binding affinity to mouse or rat VEGF). The pharmacokinetic profile of bevacizumab in cynomolgus monkeys showed revealed lower exposure, with higher clearance and shorter half-live than observed in human subjects. The elimination half-life in monkeys ranged from 8-10 days, approximately half that observed in clinical studies (half-life 20 days [range 11-50 days], and clearance was faster (4.76-5.78 mL/kg/day in monkeys as compared to approximately 3.34 mL/kg/day in population pharmacokinetic analysis).

VEGF is a regulator of angiogenesis. It is critical for growth and development of vascular and lymphatic endothelial cells. VEGF is also critical for embryonic vasculogenesis, bone formation, and the physiology of the female reproductive tract, all processes dependent upon proliferation of new blood vessels.

The administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in antitumor activity in human cancers, including colon, breast, pancreas, and prostate. Metastatic disease progression was inhibited, and microvascular permeability was reduced.

11

<u>CMC</u>
(See reviews by Carolyn Renshaw and by Michelle Frazier- Jessen Ph.D. & Joe Kutza, Ph.D.)

Bevacizumab is a [   ] IgG1 [   ] isotype monoclonal antibody [

_____   ,   ,   ] the
manufacture of bevacizumab (Bevacizumab™) 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.

The pre-approval inspection (PAI) for Bevacizumab 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." All members of the review team concurred with waiver of the pre-approval inspection.

Issues requiring further evaluation (under agreed upon post-marketing commitments) are
- Development of a validated, highly sensitive and accurate assay for the detection of an immune response (binding antibodies) to Bevacizumab and characterization of the immune response in patients receiving Bevacizumab.

- Revision of release and shelf-life specifications for drug substance and drug product based upon tolerance intervals on a yearly basis to reflect increased manufacturing experience.

- Maintain on stability the ⎯ mg vialed drug products to the intended length of expiry in order in support of the length of expiry of the 400 mg drug product configuration.

- Revision of the stability protocol to include both 100 mg and 400 mg vialed drug products for each year that Bevacizumab is produced at the South San Francisco manufacturing facility.

- Perform *in vitro* and *in vivo* viral and adventitious agent testing per ICH Q5A on a future full scale cGMP batch of Bevacizumab at the ⎯ proposed limit of *in vitro* cell age per ICH Q5A.

- Perform genetic stability testing per ICH Q5B on a future full scale cGMP batch of Bevacizumab at . ⎯ proposed limit of *in vitro* cell age.

<u>Proprietary name review</u>
The Division of Medication Errors and Technical Support (DMETS) reviewed and has no objections to the proposed proprietary name Bevacizumab. Recommendations by DMETS were considered in final labeling (package insert and carton/container labeling).

<u>Labeling review</u>
A number of modifications to the proposed labeling were recommended by FDA and accepted by Genentech, including removal of ⌐

⌐ and the addition of the preliminary results of NCI Intergroup study to the Clinical Studies section, demonstrating lack of efficacy of single agent bevacizumab as compared to combination chemotherapy. The preliminary results of the NCI treatment protocol of Avastin, 5-FU, and leucovorin, showing an absence of anti-tumor activity (overall response rate <5%) in patients receiving third-line chemotherapy for metastatic colorectal cancer were not available in sufficient detail to permit inclusion in the label.

The requested claim was modified in light of several pieces of information. The indication proposed by Genentech was:
   "AVASTIN (bevacizumab) ⌐   ⌐
   is indicated for first-line treatment of patients with metastatic carcinoma of the colon and rectum."

First, the request for use ⌐   ⌐ " was modified to read "in combination with intravenous 5-fluorouracil-based chemotherapy" based on the lack of benefit observed in the study of Avastin in combination with Xeloda (on oral 5-FU prodrug) in second- and third-line treatment of metastatic breast cancer and the potential for drug-drug interactions between Xeloda and Avastin that have been raised as possible explanations for this observed lack of activity. The indication was not restricted to the regimen of IFL (as used in AVF2107g) for several reasons. First, enhanced efficacy was also observed in the first-line setting when Avastin was added to 5-FU and leucovorin without irinotecan. In addition, due to concerns regarding toxicity and significant improvements in survival observed with FOLFOX4, 5-flourouracil-oxaliplatin based chemotherapy is becoming a standard first-line treatment regimen, while IFL is reserved for second-line therapy. While studies investigating whether Avastin, in combination with FOLFOX, provides additional benefit are ongoing, there is no evidence that Avastin results in unacceptably increased toxicity when used in combination with FOLFOX (as in E3200). Pending the results of controlled studies ruling out a benefit from the addition of Avastin to FOLFOX, it is reasonable to conclude that Avastin has the potential to benefit all patients receiving first-line therapy and should be available for use in that population.

<u>Recommendation:</u>
The following application is recommended for approval by all members of the review team. I concur with review team and also recommend approval for this application.