



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of Paul J. CARTER, *et al.*

Patent No. 6,054,297

Attorney Docket No. 22338-40130

Issued April 25, 2000

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir:

Applicant, Genentech, Inc., hereby submits this application for extension of the term of United States Letters Patent No. 6,054,297 under 35 U.S.C. § 156 by providing the following information in accordance with the requirements specified in 37 C.F.R. § 1.740.

Applicant represents that it is the assignee of the entire interest in and to United States Letters Patent No. 6,054,297 granted to Paul J. Carter and Leonard G. Presta (Carter *et al.*) by virtue of an assignment of such patent to Genentech, Inc., recorded October 5, 1992, at Reel 006364, Frame 0946.¹

1. Identification of the Approved Product [§ 1.740(a)(1)]

The name of the approved product is AVASTIN™. The name of the active ingredient of AVASTIN™ is Bevacizumab. Bevacizumab is a recombinant humanized monoclonal IgG₁ antibody which contains human framework regions (FRs) and the complementarity-determining regions (CDRs) of a murine antibody that binds to Vascular Endothelial Growth Factor (VEGF).

¹ The assignment recorded at the noted location in the Office's records identifies U.S. Patent No. 5,821,337, the immediate parent of U.S. Patent No. 6,054,297. The conveyance includes the entire right, title, and interest in the continuation application upon which the '297 patent was granted.

2004 E-0402

APP 1

**2. Federal Statute Governing Regulatory Approval of the Approved Product
[§ 1.740(a)(2)]**

The approved product was subject to regulatory review under, *inter alia*, the Public Health Service Act (42 U.S.C. § 201 *et seq.*) and the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355 *et seq.*).

3. Date of Approval for Commercial Marketing [§ 1.740(a)(3)]

AVASTIN™ was approved for commercial marketing or use under § 351 of the Public Health Service Act on **February 26, 2004**.

4. Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]

- (a) The active ingredient of AVASTIN™ is Bevacizumab. Bevacizumab is a humanized monoclonal IgG₁ antibody produced in a Chinese Hamster Ovary mammalian cell expression system. It contains human framework regions (FRs) and the complementarity-determining regions (CDRs) of a murine antibody that binds to VEGF.
- (b) Applicant certifies that Bevacizumab has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act prior to the approval granted on February 26, 2004 to the present Applicant.
- (c) Bevacizumab has been approved for use in combination with intravenous 5-fluorouracil-based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon or rectum. *See* AVASTIN™ product label, provided as Attachment C.
- (d) AVASTIN™ was approved for commercial marketing pursuant to § 351 of the Public Health Service Act (42 U.S.C. § 262) under Genentech's existing Department of Health and Human Services (DHHS) U.S. License No. 1048. *See* AVASTIN™ approval letter, provided as Attachment D.

5. Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]

Applicant certifies that this application for patent term extension is being submitted within the sixty (60) day period permitted for submission specified in 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f). The last date on which this application may be submitted is April 26, 2004.

6. Complete Identification of the Patent for Which Extension Is Being Sought [§ 1.740(a)(6)]

The complete identification of the patent for which an extension is being sought is as follows:

- (a) Names of the inventors: Paul J. Carter and Leonard G. Presta
- (b) Patent Number: 6,054,297
- (c) Date of Issue: April 25, 2000
- (d) Date of Expiration: April 25, 2017

7. Copy of the Patent for Which an Extension is Being Sought [§ 1.740(a)(7)]

A copy of U.S. Patent No. 6,054,297 is provided as Attachment F to the present application.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]

- (a) U.S. Patent No. 6,054,297 is not subject to a terminal disclaimer.
- (b) No certificate of correction has been issued for U.S. Patent No. 6,054,297.
- (c) The first maintenance fee for U.S. Patent No. 6,054,297, due on October 25, 2003, has been paid. A copy of the maintenance fee statement showing that the fee was timely paid is provided as Attachment G. The next maintenance fee will be due on October 25, 2007.
- (d) U.S. Patent No. 6,054,297 has not been the subject of a reexamination proceeding.

9. Statement Regarding Patent Claims Relative to Approved Product [§ 1.740(a)(9)]

The statements below are made solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). Applicant notes that, as the M.P.E.P. acknowledges, § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

- (a) At least the following claims of U.S. Patent No. 6,054,297 (“the ‘297 patent”) claim the active pharmaceutical ingredient in the approved product or a method that may be used to make that ingredient: claims 1, 6, 7, 8, 9, 10, 12, 29, and 30.
- (b) Pursuant to M.P.E.P. § 2753 and 37 C.F.R. § 1.740(a)(9), the following explanation is provided which shows how the above-listed claims of the patent claim the approved product or a method of making the approved product.

(1) *Description of the approved product and its method of production*

The approved product is described as follows in the approved label for AVASTIN™, a copy of which is provided as Attachment C.

AVASTIN™ (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 [citation to L.G. Presta *et al.* (1997) *Cancer Res.* 57: 4593-99, provided as Attachment B]. Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 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. The 400 mg product is formulated in 960 mg α,α -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.

The Presta *et al.*, paper cited in the approved label describes examples of humanizing the murine antibody structure upon which the structure of Bevacizumab is based. It also describes the interaction of the variable domains of the humanized antibodies with the antigen, VEGF. It discloses, *inter alia*, binding data for a humanized F(ab) antibody fragment, “F(ab)-12.” In addition to non-human CDRs derived from the sequence of the murine antibody, Bevacizumab comprises framework substitutions in the variable domains at position 46 in the light chain (V_L) and positions 49, 69, 71, 73, 76, 78 and 94 in the heavy chain (V_H) that are the same as the substitutions shown at the corresponding positions of F(ab)-12, as shown in Fig. 1 of Presta *et al.* (provided as Attachment A). Presta *et*

al. provides information concerning the molecular characteristics and binding properties of the active pharmaceutical ingredient, Bevacizumab, present in AVASTIN™.

(2) *Claims 9, 10, 29, and 30*

Claims 9, 10, 29, and 30 of the '297 patent, each directed to a product, read as follows.

9. A humanized antibody variable domain having a functional antigen binding region, said humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues incorporated into a V_H subgroup III consensus human antibody variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of:
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 92H, and 93H.
10. The humanized antibody variable domain of claim 9, wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.
29. An antibody which binds an antigen and comprises non-human heavy chain variable domain Complementarity Determining Region (CDR) amino acid residues which bind said antigen and V_H subgroup III consensus human variable domain Framework Region (FR) amino acid residues; and further comprises non-human light chain variable domain CDR amino acid residues which bind said antigen.
30. The antibody of claim 29, further comprising V_L κ subgroup I consensus human variable domain FR amino acid residues.

As explained below, the active pharmaceutical ingredient of the approved product, Bevacizumab, is a humanized monoclonal antibody that meets the limitations of claims 9, 10, 29, and 30.

Comparison of Bevacizumab to claim 9

The amino acid sequences of the V_L and V_H domains² of Bevacizumab comprise FR substitutions at positions 46L, 49H, 69H, 71H, 73H, 76H, 78H and 94H that are identical to the substitutions at the corresponding positions of the “F(ab)-12” sequences shown in Figure 1 (provided as Attachment A).³ Of these, substitutions at positions 46L, 49H, 69H, 73H, 76H, and 78H are within the substitutions specified in the Markush group of claim 9. In the manner of Figure 5 of the '297 patent, Attachment A also shows the sequences of the same import antibody (“A4.6.1”) used to design Bevacizumab on the lines above the F(ab)-12 sequences and of Kabat consensus sequences (“humIII”) below.⁴ The human consensus heavy chain variable domain (V_H) sequence upon which the V_H sequence of Bevacizumab is based is a subgroup III sequence. The A4.6.1 antibody is a murine monoclonal antibody; its sequence is therefore “non-human.” See the approved label for AVASTIN™, provided as Attachment C.

As shown in Figure 1 (Attachment A), in each of the V_L and V_H domains of Bevacizumab “substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species” (*i.e.*, the murine antibody A4.6.1). See '297 at col. 2, lines 27-31. Also, the variable domains in Bevacizumab are linked to other polypeptide structures (in this case, constant region sequences of a human IgG subtype antibody). See, for example, AVASTIN™ label, Attachment C, and '297 at col. 12, lines 10-43. Bevacizumab is therefore a “humanized antibody” within the meaning of the '297 patent.

The V_H domain of Bevacizumab comprises non-human amino acid residues in its CDRs. The CDRs of the variable domains in Bevacizumab comprise functional “antigen-binding region[s]” that bind to the human VEGF protein. See AVASTIN™ label, provided as Attachment C.

² Naturally occurring antibodies comprise two identical immunoglobulin (Ig) “light” chains and two identical Ig “heavy” chains having defined amino acid sequences. The light and heavy chains each comprise single “variable” regions designated V_L and V_H , respectively. See '297 at col. 1, lines 18-32.

³ The figure provided as Attachment A is Fig. 1 from Presta *et al.*, *Cancer Res.* (1997).

⁴ The residues in a human Ig sequence that are substituted with residues from an “import antibody” are identified according to standard numbering conventions published by Kabat. See '297 at col. 11, first full paragraph, through col. 12, paragraph bridging from col. 11. The Kabat sequences represent consensus amino acid sequences for various human antibodies in each subclass. See *id.* The '297 patent identifies residues in the Kabat sequences by a residue number and ‘L’ or ‘H,’ for residues in the V_L or V_H domains, respectively (*e.g.*, 4L, 36H). The figure provided as Attachment A also uses the conventional Kabat numbering.

Comparison of Bevacizumab to claim 10

Each of the amino acid residues present at positions 46L, 49H, 69H, 73H, 76H, and 78H in Bevacizumab is identical to the residue present at the corresponding position in the murine import antibody, A4.6.1. Bevacizumab thus meets the additional limitation of claim 10.

Comparison of Bevacizumab to claim 29

As discussed above in connection with claim 9, Bevacizumab is an antibody; it binds the VEGF antigen via the amino acid residues in its CDRs; and it comprises FR residues of a human consensus V_H subgroup III sequence. Bevacizumab additionally comprises a light chain that includes variable domain (V_L) CDRs that participate in antigen binding. Bevacizumab thus meets all of the limitations of claim 29.

Comparison of Bevacizumab to claim 30

The human consensus V_L domain sequence from which the light chain FR sequences of Bevacizumab are derived is a human κ subgroup I (κI) sequence. Bevacizumab thus meets the additional limitation of claim 30.

Conclusion

Because Bevacizumab meets all of the limitations of each of claims 9, 10, 29, and 30 of the '297 patent, and because Bevacizumab is present in AVASTIN™, claims 9, 10, 29, and 30 of U.S. Patent No. 6,054,297 cover the approved product.

(3) *Claims 1, 6, 7, 8, and 12*

Claims 1, 6, 7, 8 and 12 of the '297 patent, each directed to a method of making a product, read as follows.

1. A method for making a humanized antibody comprising non-human, import Complementarity Determining Region (CDR) amino acid residues and human Framework Region (FR) amino acid residues, comprising the steps of:
 - (a) obtaining the amino acid sequences of an import variable domain and of a V_H subgroup III consensus human variable domain;
 - (b) identifying CDR amino acid sequences in the import and the human variable domain sequences;
 - (c) substituting import CDRs for the corresponding human CDRs;

- (d) aligning the amino acid sequences of a FR of the import antibody and the corresponding FR of the consensus variable domain;
 - (e) identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus variable domain residues;
 - (f) determining if the non-homologous import amino acid residue is expected to have at least one of the following effects:
 - (1) non-covalently binds antigen directly;
 - (2) interacts with a CDR; or
 - (3) participates in the V_L - V_H interface;
 - (g) for any non-homologous import antibody amino acid residue which is expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus variable domain FR sequence; and
 - (h) preparing a humanized antibody which binds antigen, wherein the humanized antibody comprises an amino acid sequence determined according to the above steps.
6. The method of claim 1, wherein the corresponding consensus residues are selected from the group consisting of 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
7. A method for making a humanized antibody comprising non-human Complementarity Determining Region (CDR) amino acid residues and human Framework Region (FR) amino acid residues, comprising providing an import, non-human antibody variable domain amino acid sequence having CDR amino acid residues and FR amino acid residues; obtaining the amino acid sequence of a V_H subgroup III consensus human antibody variable domain having CDR amino acid residues and FR amino acid residues; substituting non-human CDR amino acid residues for human CDR amino acid residues in the consensus human antibody variable domain; substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H,

78H, 91H, 92H, 93H, and 103H; and preparing a humanized antibody which binds an antigen, wherein the humanized antibody comprises an amino acid sequence determined according to the above steps.

8. The method of claim 7, wherein the substituted residue is the residue found at the corresponding location of the non-human antibody.
12. A method for making a humanized antibody comprising introducing Complementarity Determining Region (CDR) amino acid residues from an import antibody variable domain into a V_H subgroup III consensus human antibody variable domain.

Comparison of Bevacizumab to claim 1

As discussed above with respect to claim 9, Bevacizumab is a humanized antibody comprising non-human Complementarity Determining Region (CDR) amino acid residues and human Framework Region (FR) amino acid residues, as the preamble of claim 1 requires.

In the manner illustrated in Figure 1 (provided as Attachment A), Bevacizumab, incorporates residues found in the V_L and V_H domains of the murine monoclonal antibody, A4.6.1, into corresponding consensus sequences of human Ig variable domains. *See also* the approved label for AVASTIN™, provided as Attachment C. Ig variable domains necessarily comprise CDR and FR sequence elements. Thus, selecting the V_H domain of the A4.6.1 murine antibody and a Kabat consensus V_H subgroup III sequence meets the limitation of “(a) obtaining the amino acid sequences of an import variable domain and of a V_H subgroup III ... domain” because the Kabat sequence upon which the sequence of Bevacizumab is based is a V_H subgroup III sequence.

The scheme for humanizing murine antibody A4.6.1, shown in the figure of Attachment A, demonstrates that a humanized antibody sequence may be obtained by “(b) identifying CDR ... sequences” and “(c) substituting import CDRs,” as claim 7 requires. Also as seen from the figure, the choice of divergent FR residues from the aligned A4.6.1 sequence into the V_H consensus sequence at positions 49H, 69H, 73H, 76H, and 78H meets the “(d) aligning,” and “(e) identifying” steps of claim 1. Because Bevacizumab comprises the substitutions illustrated in the figure at these positions, an analogous scheme for designing Bevacizumab will meet these claim limitations.

The FR residues at (at least) positions 46L, 49H, 69H, 71H, 73H, 76H 78H and 94H of Bevacizumab are expected to bind VEGF, interact with a CDR, and/or participate in the V_L - V_H interface. *See, e.g.,* Presta *et al.* at 4596, paragraph

bridging to 4597, and 4597, paragraph bridging columns. Accordingly, the choice and substitution of any of these residues meets the limitations of “(f) determining” and “(g) substituting” as required by claim 1. Finally, Bevacizumab binds to an antigen, VEGF. *See* approved label for AVASTIN™, Attachment C. Because the “(h) preparing” step of claim 7 is generic, any method of producing Bevacizumab meets the “preparing” limitation of the claim. Accordingly, all of the limitations of claim 1 are met.

Comparison of Bevacizumab to claim 6

As noted above, Bevacizumab comprises FR substitutions at positions 46L, 49H, 69H, 73H, 76H, and 78H. These positions are among those recited in the Markush group of claim 6. Claim 6 permits more than one of the recited substitutions in a single molecule, and the claimed method permits substitutions at positions other than those recited. As such, all of the limitations of dependent claim 6 are met.

Comparison of Bevacizumab to claim 7

As discussed above, Bevacizumab is a humanized antibody comprising non-human Complementarity Determining Region (CDR) amino acid residues and human Framework Region (FR) amino acid residues, as the preamble of claim 7 requires.

In the manner shown in the figure provided as Attachment A, Bevacizumab incorporates residues found in the V_L and V_H domains of the murine monoclonal antibody, A4.6.1, into corresponding consensus sequences of human Ig variable domains. *See*, the approved label for AVASTIN™, provided as Attachment C. Because Ig variable domains necessarily comprise CDR and FR sequence elements, selecting the A4.6.1 murine antibody and the amino acid sequence of its V_H domain meets the limitation of “providing an import, non-human antibody variable domain amino acid sequence having CDR amino acid residues and FR amino acid residues.” Selecting the Kabat consensus V_H subgroup III sequence used to design the V_H sequence of Bevacizumab meets the limitation of “obtaining the sequence of a V_H subgroup III ... domain.”

In the manner shown in Figure 1 (Attachment A), the humanized antibody sequence of Bevacizumab may be obtained by “substituting CDR residues,” as claim 7 requires. Similarly, the substitution of residues from the A4.6.1 sequence into the V_H consensus sequence at positions 46L, 49H, 69H, 73H, 76H, and 78H meets the “substituting” step of claim 7 with respect to one or more of the specified Markush group elements. Bevacizumab binds to an antigen, VEGF. *See* approved label for AVASTIN™, Attachment C. And because the “preparing”

step of claim 7 is generic, any method of producing Bevacizumab meets the “preparing” limitation of the claim.

Comparison of Bevacizumab to claim 8

Each of the amino acid residues present at positions 46L, 49H, 69H, 73H, 76H, and 78H in Bevacizumab is identical to the residue present at the corresponding position in the murine import antibody, A4.6.1. Bevacizumab thus meets the additional limitation of claim 8.

Comparison of Bevacizumab to claim 12

As discussed above, the heavy chain variable domain of Bevacizumab comprises substitutions from the sequence of an import antibody, A4.6.1, at corresponding positions in a V_H subgroup III consensus human antibody variable domain sequence. Thus, Bevacizumab meets all of the limitations of the products specified in claim 12, and Bevacizumab may be produced by the method claimed.

Conclusion

Because methods that may be used to design and produce Bevacizumab meet all of the material and functional limitations of claims 1, 6, 7, 8, and 12 of the '297 patent, and because producing Bevacizumab is an integral step in making the approved product, AVASTIN™, claims 1, 6, 7, 8, and 12 of U.S. Patent No. 6,054,297 cover the approved product.

10. Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [§ 1.740(a)(10)]

(a) Patent Issue Date

U.S. Patent No. 6,054,297 was issued on April 25, 2000.

(b) IND Effective Date [35 U.S.C. § 156(g)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(A)]

The date that an exemption under § 505(i) of the Federal Food, Drug and Cosmetic Act became effective (*i.e.*, the date that an investigational new drug application (“IND”) became effective) for AVASTIN™ (originally referred to as “rhuMab VEGF”) was February 3, 1997. The IND was assigned number BB-IND # 7023. A copy of the letter from the FDA reflecting the effective date of the IND is provided in Attachment E. The application date for this IND was January 31, 1997.

(c) BLA Submission Date [35 U.S.C. § 156(g)(1)(B)(i); 37 C.F.R. § 1.740(a)(10)(i)(B)]

The BLA was submitted on a rolling basis pursuant to FDA’s letter dated August 28, 2003. Accordingly, initial portions of the BLA were submitted by Genentech to the FDA on August 29, 2003.⁵ A second submission was made on September 15 and the final submission was made on September 25. The BLA was assigned number BLA 125085/0. In a letter dated November 28, 2003, FDA indicated that it had completed an initial review of the application dated September 25, 2003 and, according to 21 C.F.R. 601.2(a), filed the application on the date of the letter, November 28, 2003.

(d) BLA Issue Date [35 U.S.C. § 156(g)(1)(B)(ii); 37 C.F.R. § 1.740(a)(10)(i)(C)]

The FDA approved biologic license application 125085/0 authorizing the marketing of AVASTIN™ on February 26, 2004. AVASTIN™ was approved under Department of Health and Human Services (DHHS) U.S. License No. 1048. A copy of the approval letter from the FDA is provided as Attachment D.

⁵ We have used this date in the relevant calculations as the date that the application was submitted.

11. Summary of Significant Events During Regulatory Review Period [§ 1.740(a)(11)]

Pursuant to 37 C.F.R. § 1.740(a)(11), the following provides a brief description of the activities of Genentech, Inc., before the FDA in relation to the regulatory review of AVASTIN™. The brief description lists the significant events that occurred during the regulatory review period for the approved product. In several instances, communications to or from the FDA are referenced. Pursuant to 37 C.F.R. § 1.740(a)(11), 21 C.F.R. § 60.20(a), and M.P.E.P. § 2753, copies of such communications are not provided in this application, but can be obtained from records maintained by the FDA.

- On January 31, 1997, Genentech submitted to FDA an investigational new drug application for a recombinant humanized monoclonal antibody (rhuMAb VEGF, now known as Bevacizumab) against Vascular Endothelial Growth Factor (VEGF). The antibody was developed as a potential new therapeutic in combination with chemotherapy for its effect on survival in the first-line treatment of patients with metastatic carcinoma of the colon and rectum.
- On February 3, 1997, FDA made BB-IND # 7023 effective via a communication mailed to Genentech on February 10, 1997 (see Attachment E). According to the FDA, initiation of trials could begin 30 days after February 3, 1997.
- From approximately April 14, 1997 until approximately April 7, 2003, a series of Phase I, II, and III clinical trials were conducted. In addition, an extension trial, AVF2540g, is ongoing as of the date of this application.
- On March 9, 2000, representatives of Genentech and CBER participated in an end-of-Phase II meeting.
- On July 27, 2000, representatives of Genentech and CBER participated in a pre-Phase III meeting
- Between approximately September 2000 and April 2003, Phase III clinical trials were conducted. In addition, an extension trial, AVF2540g, is ongoing as of the date of this application.
- On June 25, 2003, FDA granted fast-track designation for rhuMAb VEGF.
- On July 24, 2003 representatives of Genentech and CBER participated in a pre-BLA submission meeting to discuss information and requirements for the chemical, manufacturing and control chapter of the BLA.
- On July 25 and 27, 2003 representatives of Genentech and CBER participated in a pre-BLA submission meeting to discuss and review clinical results of trials conducted prior to that date.

- On August 28, 2003 FDA approved the timeline for the “rolling submission” and commencement of review of portions of the biologics licensing application for AVASTIN™.
- On August 29, 2003, Genentech began submitting, on a rolling basis, portions of a biologics licensing application for AVASTIN™. Genentech made a second submission on September 15 and a last submission, which completed the application, on September 25, 2003. On November 28, 2003, BLA 125085/0 was found acceptable for filing.
- On April 15, 2002 the IND was placed on partial clinical hold for Dr. Mansoor Saleh.
- On or near April 23, 2003 the clinical hold for Dr. Mansoor Saleh was removed.
- On January 14, 2003 the IND was placed on partial clinical hold for Dr. James Holland.
- On October 22, 2003 the clinical hold for Dr. James Holland was removed.
- On April 21, 2003 the IND was placed on partial clinical hold for Dr. Louis Fehrenbacher.
- On July 11, 2003 the clinical hold for Dr. Louis Fehrenbacher was removed.
- On February 26, 2004, FDA approved BLA 125085/0, issuing marketing authorization for AVASTIN™. *See Attachment D.*

12. Statement Concerning Eligibility for and Duration of Extension Sought Under 35 U.S.C. § 156 [37 C.F.R. § 1.740(a)(12)]

- (a) In the opinion of the Applicant, U.S. Patent No. 6,054,297 is eligible for an extension under § 156 because:
- (i) one or more claims of the '297 patent claim the approved product or a method of making or using the approved product;
 - (ii) the term of the '297 patent has not been previously extended on the basis of § 156;
 - (iii) the '297 patent has not expired;
 - (iv) no other patent has been extended pursuant to § 156 on the basis of the regulatory review process associated with the approved product, AVASTIN™;
 - (v) there is an eligible period of regulatory review by which the patent may be extended pursuant to § 156;
 - (vi) the applicant for marketing approval exercised due diligence within the meaning of § 156(d)(3) during the period of regulatory review;
 - (vii) the present application has been submitted within the 60-day period following the approval date of the approved product, pursuant to § 156(c); and
 - (viii) this application otherwise complies with all requirements of 35 U.S.C. § 156 and applicable rules and procedures.
- (b) The period by which the term of the '297 patent is requested by Applicant to be extended is **307 days**.
- (c) The requested period of extension of term for the '297 patent corresponds to the regulatory review period that is eligible for extension pursuant to § 156, based on the facts and circumstances of the regulatory review associated with the approved product AVASTIN™. The period was determined as follows.
- (i) The relevant dates for calculating the regulatory review period, based on the events discussed in the section above, are the following.

Exemption under FDCA § 505(i)
became effective

February 3, 1997

Patent was granted	April 25, 2000
Biologics License Application (BLA) under PHSA § 351 was filed	August 29, 2003
BLA was approved	February 26, 2004

- (ii) The '297 patent was granted during the period specified in § 156(g)(1)(B)(i) (*i.e.*, the period from the date of the grant of the exemption under § 505(i) of the FDCA until the date of submission of the BLA). Pursuant to § 156(b) and (c)(2), the calculated regulatory review period includes a component equal to half of the number of days within that period that are after the grant of the patent ($\frac{1}{2}$ of 1217, or 609 days).
- (iii) Because the patent was granted before the start of the period specified in § 156(g)(1)(B)(ii) (*i.e.*, the period from the date of submission of the BLA until the date of approval), the regulatory review period under § 156(b) includes a component equal to the total number of days in that period (181 days).
- (iv) The period determined according to § 156(b), (c)(2), and (g)(1) for the approved product is greater than 307 days.
- (v) The '297 patent will expire on April 25, 2017.
- (vi) The date of approval of the approved product is February 26, 2004.
- (vii) The date that is fourteen years from the date of approval of the approved product is February 26, 2018.
- (viii) The period measured from the date the patent expires (*i.e.*, April 25, 2017) until the end of the fourteen-year period specified in § 156(c)(3) (*i.e.*, February 26, 2018) is 307 days.
- (ix) The number of days in the regulatory review period determined pursuant to § 156(b), (c)(2), and (g)(1) exceeds the number of days that the patent may be extended pursuant to § 156(c)(3). As such, the period by which the patent may be extended is limited by the fourteen-year rule of § 156(c)(3) to a period of 307 days.
- (x) The '297 patent issued after the effective date of Public Law No. 98-417. As such, the two- or three-year limit of 35 U.S.C. § 156(g)(6)(C) does not apply.

13. Statement Pursuant to 37 C.F.R. § 1.740(a)(13)

Pursuant to 37 C.F.R. § 1.740(a)(13), Applicant acknowledges its duty to disclose to the Director of the PTO and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. § 1.765.

14. Applicable Fee [§ 1.740(a)(14)]

A check is enclosed in the amount specified pursuant to 37 C.F.R. § 1.20(j) corresponding to the fee for a patent term extension application under 35 U.S.C. § 156. Please deduct any additional fee or fees deemed necessary in excess of this amount from our deposit account no. 18-1260.

15. Name and Address for Correspondence [§ 1.740(a)(14)]

Please direct all inquiries, questions, and communications regarding this application for term extension to:

Jeffrey P. Kushan
SIDLEY AUSTIN BROWN AND WOOD LLP
1501 K Street, N.W.
Washington, D.C. 20005
Phone: 202-736-8914
Fax: 202-736-8111
email: jkushan@sidley.com

The correspondence address for U.S. Patent No. 6,054,297 is unchanged for all other purposes. An Associate Power of Attorney granted to the undersigned, a copy of which is included with this application as Attachment H, accompanies this communication.

Two additional copies of this application are enclosed, in compliance with 37 C.F.R. § 1.740(b).

Sincerely,



Jeffrey P. Kushan
Attorney for Applicant
Registration No. 43,401
SIDLEY AUSTIN BROWN AND WOOD LLP
1501 K Street, N.W.
Washington, D.C. 20005

Dated: April 23, 2004

U.S. Patent No. 6,054,297
Carter, *et al.*
Application Under 35 U.S.C. § 156

INDEX OF ATTACHMENTS

- Attachment A: Amino Acid Sequences of the Variable Domains of Bevacizumab
- Attachment B: Presta *et al.*, *Cancer Res.* (1997)
- Attachment C: AVASTIN™ Product Label
- Attachment D: AVASTIN™ Approval Letter
- Attachment E: FDA Communication Concerning Effective Date of BB-IND # 7023
- Attachment F: U.S. Patent No. 6,054,297
- Attachment G: Statement Showing Payment of First Maintenance Fee in Patent No. 6,054,297
- Attachment H: Power of Attorney