

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE : U.S. Patent No. 6,051,698
ISSUED: April 18, 2000
TO: NEBOJSA JANJIC, et al.
FOR: VASCULAR ENDOTHELIAL
GROWTH FACTOR (VEGF)
NUCLEIC ACID LIGAND
COMPLEXES
FROM: SERIAL NO. 08/897,351
OF: July 21, 1997

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REQUEST FOR EXTENSION OF THE TERM OF
UNITED STATES PATENT NO. 6,051,698 UNDER 35 U.S.C. §156

Dear Sir,

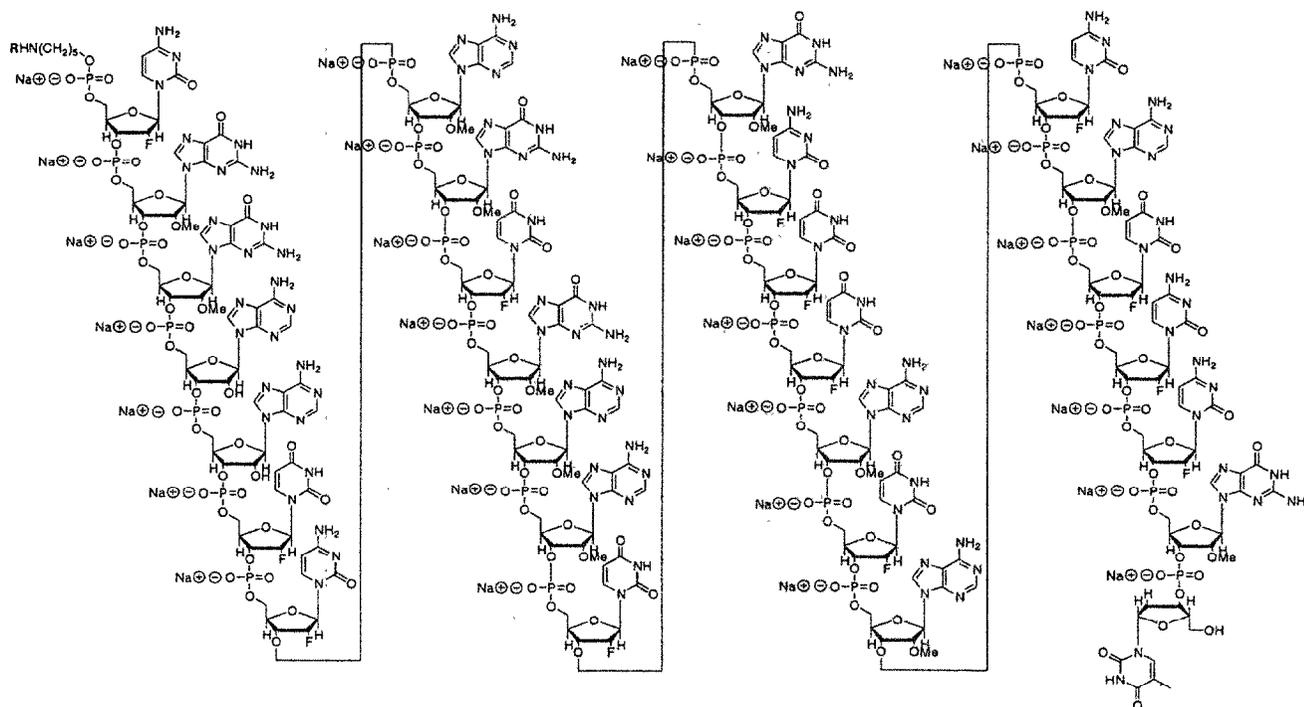
Gilead Sciences, Inc., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 333 Lakeside Drive, Foster City, CA 94404, United States of America, represents that it is the owner of the entire right, title, and interest in and to Letters Patent of the United States No. 6,051,698 granted to Nebojsa Janjic et al. on the 18th day of April, 2000, for Vascular Endothelial Growth Factor (VEGF) Nucleic Acid Ligand Complexes, subject to an exclusive license granted Eyetech Pharmaceuticals, Inc., by virtue of assignments, recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent Office") on the 17th day of November, 1997, at Reel 008887, Frame 0898 and on the 18th day of February, 2001, at Reel 011566, Frame 0868.

Pursuant to the provisions of 37 C.F.R. §1.730, applicant hereby applies for an extension of the term of Patent No. 6,051,698 under 35 U.S.C. §156 of 990 days, based on the materials set forth herein and in the accompanying papers.

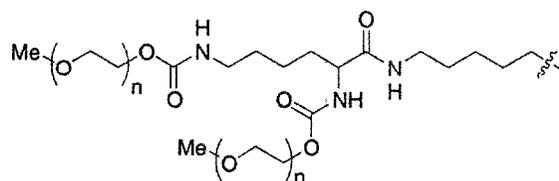
In the materials which follow herein, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. §1.740(a).

(1) The approved product is Macugen® (pegaptanib sodium injection).

Macugen® is a sterile, aqueous solution for intravitreal injection and consists of pegaptanib sodium, a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue. Pegaptanib sodium is represented by the following structural formula:



where R is:



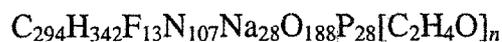
and n is approximately 450.

Chemical name:

The chemical name for pegaptanib sodium is as follows: RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2'-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT), 5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphonoxy)pentyl]amino]carbonyl]-3,13-dioxo-5,11-diaza-1,15-pentadecanediyl]bis[ω-methoxypoly(oxy-1,2-ethanediyl)], sodium salt

Molecular formula:

The molecular formula for pegaptanib sodium is



(where n is approximately 900)

Molecular Weight:

The molecular weight is approximately 50 kilodaltons.

We note that the term “product,” for purposes of patent term extension for a drug product, is defined as “the active ingredient of a new drug, antibiotic drug, or human biological product...including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.” 35 U.S.C. § 156(f)(2). Nothing in this application should be construed as limiting the term product for purposes of the requested patent term extension to the specific form of pegaptanib approved in Macugen®.

(2) Macugen® (pegaptanib sodium injection) was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act, which is codified at 21 U.S.C. §355(b).

(3) Macugen® (pegaptanib sodium injection) received permission for commercial marketing or use under section 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(b), on December 17, 2004.

(4) The active ingredient in Macugen® (pegaptanib sodium injection) is pegaptanib. That active ingredient has not been previously 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.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application could be submitted is February 15, 2005.

(6) The patent for which an extension is being sought is identified as follows:

Inventors: Nebojsa Janjic, Larry Gold, Paul Schmidt, Chandra Vargeese

Patent No.: 6,051,698

For: VASCULAR ENDOTHELIAL

GROWTH FACTOR (VEGF)

NUCLEIC ACID LIGAND COMPLEXES

Issued: April 18, 2000

Expires: October 17, 2012

(7) A copy of U.S. Patent No. 6,051,698, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) One maintenance fee payment for U.S. Patent No. 6,051,698 has been made to keep the patent in force beyond four years from its issue date (a copy of the maintenance fee statement is included herewith as EXHIBIT B). A terminal disclaimer was filed December 7, 1998 disclaiming any portion of the patent term beyond the expiration date of U.S. Patent No. 5,811,533, which in turn is subject to a terminal

disclaimer to U.S. Patent No. 5,459,015, which will expire Oct. 17, 2012 (17 years from its issuance) (copy of the terminal disclaimer filed December 7, 1998 is included herewith as EXHIBIT C).

(9) Patent No. 6,051,698 claims the approved product. Claims 1, 3-5, and 8-14 claim the approved product.

Patent No. 6,051,698 claims a method of manufacturing the approved product. Claims 2 and 16-20 claim a method of manufacturing the approved product.

Claim 1 of Patent No. 6,051,698 reads on Macugen® because:

Macugen® is a purified and isolated non-naturally occurring RNA ligand to Vascular Endothelial Growth Factor wherein said ligand is comprised of 2'fluoro (2'F)-modified nucleotides, as depicted in numbered paragraph (1) of this request.

Claim 2 of Patent No. 6,051,698 reads on a method of manufacturing Macugen® because:

Macugen®'s manufacture includes covalently linking a Non-Immunogenic, High Molecular Weight compound to a VEGF Nucleic Acid Ligand to form a complex comprised of a VEGF Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for Macugen® (pegaptanib sodium injection) on August 20, 1998, following receipt by the Food and Drug Administration of Investigational New Drug (“IND”) Application No. 56,503 on July 22, 1998.
- A New Drug Application (“NDA”) under section 505(b) of the Federal Food, Drug and Cosmetic Act for Macugen®(pegaptanib sodium injection) was completed as follows:

Reviewable Unit 1 of the NDA was submitted to FDA on March 17, 2004*

Reviewable Unit 2 of the NDA was submitted on June 17, 2004.

This NDA was assigned the number 21,756.

- NDA No. 21,756 was approved on December 17, 2004.

* Because this application was reviewed by FDA as part of its “Fast Track” program, the NDA was submitted in two stages. We believe that the first submission date constitutes the date that this application “was initially submitted” for purposes of 35 U.S.C. § 156(g). Accordingly, we have calculated the proposed period of extension on that basis. However, if it is determined that the date of the second submission is the appropriate one to be used for this purpose, forty-five days should be subtracted from the period of extension we have calculated.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities follows:

The investigational new drug application (“IND”) for this drug was submitted on July 21, 1998 and became effective on August 20, 1998. Eyetech and its predecessor sponsors of this drug pursued several investigations of the use of this drug for the treatment of age-related macular degeneration and related indications. On January 18, 2001, FDA granted fast track designation to this product. The first reviewable unit of the NDA was submitted on March 17, 2004, with a subsequent submission of the second reviewable unit on June 17, 2004. The NDA was approved on December 17, 2004.

The following chart identifies significant communications of substance with the FDA concerning this product:

<u>Date</u>	<u>Regulatory Event</u>
Jul. 21, 1998	Investigational New Drug Application (“IND”) filed
Aug. 20, 1998	IND becomes effective
Jan. 19, 1999	Submission of change in protocol 109-01
May 6, 1999	Submission of information amendment concerning toxicology issues
Jul. 1, 1999	Submission of toxicity study reports and safety study
Sep. 3, 1999	Notification of change in ownership IND to Gilead

May 19, 2000 Notification of transfer of ownership of IND to Eyetech Pharmaceuticals

Jul. 17, 2000 Submission of new protocols EOP1000 and EOP1001

Dec. 5, 2000 Request for fast track designation for age-related macular degeneration (“AMA”)

Jan. 18, 2001 FDA letter granting fast track designation

Jan. 25, 2001 Meeting with FDA concerning proposed toxicology program

Apr. 26, 2001 Pre-phase 2/3 meeting with FDA

Oct. 29, 2001 Submission of toxicity study protocol

Mar. 28, 2002 Submission of protocol EOP1003B and 1004C

Apr. 17, 2002 Submission of protocol for EOP1005

Jun. 13, 2002 Submission of revised protocols EOP1003 and EOP1004

Oct. 3, 2002 Communication from FDA assigning review of product to Center for Drug Evaluation and Research

Nov. 21, 2002 Submission of protocol EOP1006

Nov. 21, 2002 Meeting with FDA re: statistical endpoints

Feb. 4, 2003 Submission of protocol EOP1007

Feb. 24, 2003 Meeting with FDA concerning EOP1003 and EOP1004

Feb. 27, 2003 Submission of protocol amendment EOP1007

Mar 6, 2003 Submission of protocol amendment EOP1006B

Jul. 24, 2003 Submission of statistical analysis plan

Oct. 3, 2003 Meeting with FDA

Oct. 30, 2003 Meeting with FDA re: Phase 2/3 results

Dec. 3, 2003 Submission of revised protocols EOP1003E and EOP1004F

Jan. 21, 2004 Submission of revised protocol EOP1006C

Feb. 19, 2004 Meeting with FDA concerning CMC issues

Mar. 5, 2004 Request to participate in Pilot 1 program for continuous submission of NDA

Mar. 16, 2004 FDA agreement to include NDA in Pilot 1 program

Mar. 17, 2004 Submission of first reviewable unit of NDA

Apr. 14, 2004 Submission of revised protocol EOP1011B

May 12, 2004 Statistician Request for Information

May 27, 2004 Statistician Request for Information

June 7, 2004	Medical Officer & Statistician Request for Information
Jun. 17, 2004	Submission of second reviewable unit of NDA
July 14, 2004	4-Month Safety Update
July 28, 2004	Statistician Request for Information
Sept 10, 2004	CMC Information Amendment
Sept 13, 2004	CMC Drug Substance Responses
Sept, 20, 2004	CMC Drug Product Responses
Sept 22, 2004	CMC Drug Substances Responses
Sept 23, 2004	CMC Drug Substance Responses
Sept 30, 2004	CMC Drug Substance Responses
Oct 4, 2004	Response to FDA Discipline Review Letter
Oct 5, 2004	CMC Amendment – Particulate Data
Oct 6, 2004	Response to FDA Discipline Review Letter – 2 Year Data
Oct 15, 2004	CMC Amendment – Particulate Data
Oct 29, 2004	Drug Product Responses
Nov 3, 2004	Meeting with Division to discuss Controlled Bioburden Packaging

Nov 10, 2004	CMC Amendment (Updated Test Methods)
Nov 10, 2004	Response to Clinical Questions
Nov 10, 2004	Response to FDA Request for Information (Controlled Bioburden Pkg)
Nov 12, 2004	Drug Product Responses
Nov 19, 2004	Drug Product Responses
Nov 22, 2004	Response to Clinical Questions
Nov 23, 2004	Response to Drug Product Questions (Carton samples/Assembly Instructions)
Dec 1, 2004	CMC Amendment (updated test methods)
Dec 6, 2004	Provide Macugen drug product sample cartons (printed)
Dec 8, 2004	Proposed Final Label
Dec 10, 2004	Responses to Drug Product Questions/clarifications
Dec 10, 2004	Final Labeling
Dec 10, 2004	Response to Requests for Post-Approval Commitments
Dec 13, 2004	Response to Drug Product Questions
Dec 14, 2004	Response to Drug Product Comments

Dec 16, 2004 FDA agrees to allow use of 60,000 existing
Pouch A/Cartons for launch

Dec 17, 2004 Agreed upon Post-Approval commitments

Dec 17, 2004 Approval of Macugen®

(12) In the opinion of the Applicant, Patent No. 6,051,698 is eligible for an extension under 35 U.S.C. §156. The length of extension claimed is 990 days.

The length of extension of term of Patent No. 6,051,698 of 990 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.775 as follows:

- According to 37 C.F.R. §1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.775.
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of: the period of 37 C.F.R. § 1.775(c)(1), which is the number of days in the period beginning on the date the exemption under subsection 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act; and the period of 37 C.F.R. § 1.775(c)(2), which is the number of days in the period beginning on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act and ending on the date the NDA was approved. The exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective on August 20, 1998; the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act is March 17, 2004; and the NDA was approved December 17, 2004. Hence the regulatory review period under 37 C.F.R. §1.775(c) is the sum of the period from August 20, 1998 to March 17, 2004 (37 C.F.R. § 1.775(c)(1)) and the period from March 17, 2004 to December 17, 2004 (37 C.F.R. § 1.775(c)(2)). This is the sum of 2,036 days and 275 days, which is 2,311 days.
- According to 37 C.F.R. §1.775(d)(1)(i), the number of days in the periods of 37 C.F.R. § 1.775(c)(1) and 37 C.F.R. § 1.775(c)(2) which were on and before the date on which the patent issued must be subtracted from the number of days in the regulatory review period. Patent No. 6,051,698 issued on April 18, 2000. The number of days in the period of 37 C.F.R. § 1.775(c)(1) which were on or before April 18, 2000 is calculated as the time period between August 20, 1998 and April 18, 2000, which is 607 days. As the period of 37 C.F.R. § 1.775(c)(2) began after the patent issued, no days are subtracted from the period of 37 C.F.R. § 1.775(c)(2). Hence, the number of days to be subtracted

under 37 C.F.R. § 1.775(d)(1)(i) is 607 days, which gives a reduced regulatory review period of 1,704 days.

- 37 C.F.R. §1.775(d)(1)(ii) does not apply.
- According to 37 C.F.R. §1.775 (d)(1)(iii), from the regulatory review period one then subtracts one-half of the number of days remaining in the period defined in 37 C.F.R. § 1.775(c)(1) after that period is reduced in accordance with 37 C.F.R. § 1.775(d)(1)(i) and 37 C.F.R. § 1.775 (d)(1)(ii). The number of days remaining in the period defined in 37 C.F.R. § 1.775(c)(1) after that period reduced in accordance with 37 C.F.R. § 1.775(d)(1)(i) and 37 C.F.R. § 1.775 (d)(1)(ii) is 2,036 days minus 607 days which is 1,429 days (37 C.F.R. § 1.775(d)(1)(ii) does not apply). One half of this number of days is 714 days. After subtraction, this now leaves a reduced regulatory review period under 37 C.F.R. § 1.775(d)(1) of 2,311 days minus 607 days minus 714 days, which is 990 days.

- According to 37 C.F.R. §1.775(d)(2), the reduced regulatory review period of 990 days may be added to the expiration date of Patent No. 6,051,698 as adjusted by the terminal disclaimer (i.e., October 17, 2012). This gives a date of July 4, 2015.

- According to 37 C.F.R. §1.775(d)(3), 14 years may be added to the date of approval of the approved product. This gives a date of December 17, 2018.

- According to 37 C.F.R. §1.775(d)(4), the earlier of the dates of 37 C.F.R. §1.775(d)(2) and 37 C.F.R. § 1.775(d)(3) must be selected. The earlier date of these dates is July 4, 2015 (i.e., 990 days beyond the expiration date of Patent No. 6,051,698).

- The provisions of 37 C.F.R. §1.775(d)(5) apply to this application because Patent No. 6,051,698 issued after September 24, 1984. Pursuant to 37 C.F.R. §1.775(d)(5)(i), five (5) years are added to the expiration date of Patent No. 6,051,698 (October 17, 2012) giving a date of October 17, 2017. According to 37 C.F.R. §1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R. §1.775(d)(5)(i) and 37 C.F.R. §1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. §1.775(d)(4) above is July 4, 2015. Therefore, the earlier of these dates is July 4, 2015. Applicant is entitled to an extension of term of Patent No. 6,051,698 until July 4, 2015, i.e., an extension of 990 days from original expiration date of October 17, 2012.

- The provisions of 37 C.F.R. §1.775(d)(6) do not apply because Patent No. 6,051,698 issued on April 18, 2000, which is after September 24, 1984.

(13) Applicant acknowledges a duty to disclose to the Director of United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought to the term of Patent No. 6,051,698.

(14) A check for the prescribed fee of \$1,120 under 37 C.F.R. §1.20(j) for receiving and acting on this application for patent term extension is enclosed. Any underpayment, or any additional fee that may be required, is to be charged to Deposit Account No. 19-5117 as requested in the enclosed transmittal letter.

(15) Please direct all inquiries and correspondence relating to this application for patent term extensions as follows:

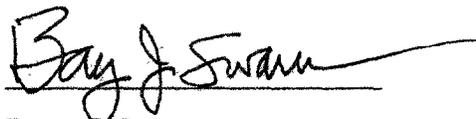
Barry J. Swanson
Swanson & Bratschun, LLC
1745 Shea Center Drive #330
Highlands Ranch, CO 80129
Ph: 303-268-0066
Fax: 303-268-0065

Pursuant to 37 C.F.R. §1.740(b), two duplicate copies of these application papers are enclosed herewith. Pursuant to M.P.E.P. §2753 an additional two copies of the application are also enclosed herewith. Accordingly, a total of four copies of the application and one original application for patent term extension of Patent No. 6,051,698 are submitted herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Letters Patent No. 6,051,698 of 990 days, based on the regulatory review period for Macugen® (pegaptanib sodium injection). The undersigned is a registered practitioner of record in the patent and is acting on behalf of the patent owner, Gilead Sciences, Inc. See 37 C.F.R. § 1.730(b)(2).

Date: February 1, 2005

Respectfully submitted,

A handwritten signature in black ink, reading "Barry J. Swanson", written over a horizontal line.

Barry J. Swanson

Attorney for Applicant

Reg. No. 33,215

IN RE: REQUEST FOR EXTENSION OF THE TERM OF UNITED STATES PATENT
NO. 6,051,698 UNDER 35 U.S.C. §156

EXHIBITS A-C

EXHIBIT A: US Patent No. 6,051,698

EXHIBIT B: Maintenance fee payment for US Patent No. 6,051,698

EXHIBIT C: Terminal Disclaimer for US Patent No. 6,051,698