OIPE IAP50
SEP 14 2005
PATENT & TRADEMARK OFFICE

Atty. Dkt. No. 355492-1300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: GREFF, et al.

Title: COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS

Patent No.: 5,667,767

Issue Date: 9/16/1997

Ser. No.: 08/507,863

Filing Date: 7/27/1995

CERTIFICATE OF EXPRESS MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service's "Express Mail Post Office To Addressee" service under 37 C.F.R. § 1.10 on the date indicated below and is addressed to: Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

EV 643 730 754 US (Express Mail Label Number) September 14, 2005 (Date of Deposit)

Laura DiStefano (Printed Name)

(Signature)

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

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP PATENT EXT.

Sir:

Applicant, Micro Therapeutics, Inc., a corporation of the State of Delaware, represents that it is the assignee of the entire interest in and to letters patent of the United States No. 5,667,767 granted to Richard J. Greff, et al. on September 16, 1997 for COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS, by virtue of an assignment in favor of Micro Therapeutics, Inc. recorded on September 26, 1995 at Reel 7699 and Frame 0014.

Applicant submits this Application for extension of the patent term for U.S. Patent 5,667,767 by providing the following information, as required by 35 U.S.C. § 156

COPY

and 37 C.F.R. § 1.710 *et seq.* For the convenience of the U.S. Patent & Trademark Office, the information in this application will be organized corresponding to 37 C.F.R. § 1.740.

1. The approved product is identified as Onyx® Liquid Embolic System (LES). The device is a kit indicated for presurgical embolization of brain arteriovenous malformations. Onyx® LES consists of a 1.5 mL vial of the Onyx® composition, a 1.5 mL vial of dimethylsulfoxide (DMSO), and three 1 mL Onyx® delivery syringes.

The composition included in the kit is referred to herein as Onyx®. The injected composition is a non-adhesive liquid embolic agent comprised of ethylene vinyl alcohol (EVOH) copolymer dissolved in DMSO, and suspended micronized tantalum. The EVOH copolymer contains approximately 48 mole percent of ethylene and 52 mole percent of vinyl alcohol. Onyx® may be one of two compositions as follows, namely Onyx® 18 and Onyx® 34:

a. Onyx® 18: 3.2 weight percent EVOH; 38.6 weight percent of tantalum; 58.2 weight percent of DMSO. Onyx® 18 has a nominal viscosity of 18 centistokes at 40°C.

b. Onyx® 34: 4.2 weight percent EVOH; 38.2 weight percent of tantalum; 57.6 weight percent of DMSO. Onyx® 34 has a nominal viscosity of 33 centistokes at 40°C.

2. Onyx® LES was subject to regulatory review under Section 515 of the Federal Food, Drug, and Cosmetic Act.

3. Onyx® LES received permission for commercial marketing under Section 515 of the Federal Food, Drug, and Cosmetic Act on July 21, 2005.

4. Onyx® Liquid Embolic System (LES) contains the Onyx® composition as described above in item 1 above. This composition for use in embolizing blood vessels has not been previously approved for commercial marketing under Section 515 of the Federal Food, Drug, and Cosmetic Act.

5. This Application for extension of patent term is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f); said period will expire on September 19, 2005.

6. The patent for which patent term extension is sought is U.S. Patent 5,667,767.

Inventors: Richard J. Greff, et al.
Patent No.: 5,667,767
Issued: September 16, 1997
Expiration Date: July 27, 2015 based on a filing date of July 27, 1995.

7. A complete copy of U.S. Patent 5,667,767 is attached hereto as Appendix A.

8. There has been no disclaimer, certificate of correction, or reexamination certificate issued in regard to U.S. Patent 5,667,767. The first maintenance fee was paid on March 16, 2001 for which a receipt is attached hereto as Appendix B. The second maintenance fee was paid on January 3, 2005 for which a receipt is attached hereto as Appendix C.

9. U.S. Patent 5,667,767 claims the approved product in the following applicable claims:

Claim 1 recites the approved product. Specifically, claim 1 recites the Onyx® composition comprising three components. All of the weight percents recited in this claim are based on the total weight of the composition.

One component of the composition is the ethylene vinyl alcohol copolymer. This copolymer is present in an amount from about 2.5 to about 8.0 weight percent of an ethylene vinyl alcohol copolymer. The amount of ethylene vinyl alcohol copolymer present in Onyx® is 3.2 (Onyx® 18) or 4.2 (Onyx® 34) weight percent and thus the amount of the polymer in the approved product falls within the claimed range.

Another component of the composition of claim 1 is a water insoluble contrast agent. The contrast agent may be tantalum, tantalum oxide and barium sulfate and is present in the amount of from about 10 to about 40 weight percent. The amount of tantalum in the approved product is 38.6 (Onyx® 18) and 38.2 (Onyx® 34) weight percent and thus falls within the claimed range.

Still another component of the composition of claim 1 is a biocompatible solvent which is present in an amount of from about 52 to about 87.5 weight percent. Turning to the specification, the biocompatible solvent can be DMSO as illustrated in column 5, line 13. The amount of DMSO in the approved product is 58.2 (Onyx® 18) and 57.6 (Onyx® 34) weight percent and thus falls within the claimed range.

Claim 2 recites the ethylene vinyl alcohol copolymer of claim 1, wherein the copolymer is from about 25 to about 60 mole percent of ethylene and from about 40 to about 75 mole percent

of vinyl alcohol in the Onyx® composition. Thus, the product described above is claimed in claim 2.

Claim 3 recites the biocompatible solvent of claim 1, wherein the solvent is DMSO. Thus, the product described above is claimed in claim 3.

Claim 4 recites the contrast agent of claim 1, wherein the contrast agent is tantalum. Thus, the product described above is claimed in claim 4.

Claim 7 covers the method of using the approved product. Specifically, claim 7 recites a method of embolizing a blood vessel by injecting an embolizing composition into the blood vessel under such conditions wherein a precipitate is formed which embolizes the blood vessel. The composition recites the following components: 2.5 to about 8.0 weight percent of an ethylene vinyl alcohol copolymer embolizing agent; from about 10 to about 40 weight percent of a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate; and from about 52 to about 87.5 weight percent of a biocompatible solvent. All of the weight percents are based upon the total weight of the composition. As detailed above, this composition employed in the method of claim 7 recites the composition in the approved product.

The composition acts to embolize the blood vessel by forming a precipitate in the blood vessel in the following manner. The copolymer is soluble in DMSO and insoluble in blood and the DMSO is miscible in blood. Therefore, when the composition is injected into the blood vessel, the DMSO dissipates into the blood and the copolymer forms a precipitate thereby embolizing the blood vessel.

Claim 8 recites the copolymer of claim 7, wherein the copolymer is from about 25 to about 60 mole percent of ethylene and from about 40 to about 75 mole percent of vinyl alcohol in the Onyx® composition. Thus, the method of using the product described above is claimed in claim 8.

Claim 9 recites the biocompatible solvent of claim 7, wherein the solvent is DMSO. Thus, the method of using the product described above is claimed in claim 9.

Claim 10 recites the contrast agent, wherein the contrast agent is tantalum. Thus, the method of using the product described above is claimed in claim 10.

Claim 13 recites that the composition is injected into the blood vessel at a rate of about 0.05 to 0.3 cc/minute. According to the product labeling of the approved product, the composition should be injected at a rate of no more than 0.3 milliliters/minute (cc/minute). Thus, the method of using the product described above is claimed in claim 13.

10. The relevant dates and information pursuant to 35 U.S.C. § 156(g) are as follows:

(A) December 14, 2000 – Effective date of IDE G000296.

(B) March 12, 2003 – PMA P030004 initially submitted to FDA.

(C) July 21, 2005 – PMA P030004 approved by FDA.

11. A detailed description of significant activities undertaken by applicant during the applicant regulatory review period is appended hereto as Appendix D and E, and incorporated herein by reference.

Appendix D is the chronology of IDE G000296. Appendix E is the chronology of PMA P030004. Both chronologies are organized in the same manner. Specifically, the communications to the FDA are listed on the left-hand side of the paper and the FDA responses are listed on the right-hand side of the paper.

12. In the opinion of the applicant, the patent is eligible for the requested extension.

Statement of Eligibility of the Patent for Extension

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if the requirements (1)-(5) are satisfied.

> (1) [T]he term of the patent has not expired before an application for extension is submitted.

The term of U.S. Patent 5,667,767 is currently set to expire on July 27, 2015. This application has been submitted before the expiration of the patent term. Accordingly, this requirement is satisfied.

> (2) [T]he term of the patent has never been extended.

The term of U.S. Patent 5,667,767 has never been extended. Accordingly, this requirement is satisfied.

> (3) [T]he application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d).

This application is submitted by an agent of the owner of record, Micro Therapeutics, Inc. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty day period beginning on the date that the approved product received permission for commercial marketing and use and contains the information required by 35 U.S.C. § 156(d). Accordingly, this requirement is satisfied.

> (4) [T]he product has been submitted to a regulatory review period before its commercial marketing or use.

The approved product was subject to regulatory review under Section 515 of the Federal Food, Drug, and Cosmetic Act by filing IDE G000296 on November 10, 2000 and PMA P030004 on March 12, 2003. Accordingly, this requirement is satisfied.

> (5) [T]he permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

The permission for the commercial marketing and use of the Onyx® LES for use in presurgical embolization of brain arteriovenous malformations granted in July 21, 2005, after regulatory review under Section 515 is the first permitted commercial marketing or use of the product in the United States. Accordingly, this requirement is satisfied.

As noted above, all of the requirements of 35 U.S.C. § 156(a) have been satisfied and thus, this patent is eligible for an extension.

Statement as to the Length of Extension Claimed

The term of U.S. Patent 5,667,767 should be extended **1,271 days**, or until **January 18, 2018** (including the additional day due to the leap year). This term of extension was determined on the following basis:

As set forth in 35 U.S.C. § 156 (g)(3)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

> (i) the period beginning on the date a clinical investigation on humans involving the device was begun and ending on the date an application was initially submitted with respect to the device under section 515, and

> (ii) the period beginning on the date an application was initially submitted with respect to the device under section 515 and ending on the date such application was approved under such Act or the period beginning on the date a notice of completion of a product development protocol was initially submitted under section 515(f)(5) and ending on the date the protocol was declared completed under section 515(f)(6).

The regulatory review period started on December 14, 2000, the day that IDE G000296 became effective. An application was initially submitted with respect to the device under section 515 on March 12, 2003. The number of days from December 14, 2000 to March 12, 2003 was 818 days. The application was approved under such Act was July 21, 2005. The number of days from March 12, 2003 to July 21, 2005 was 862 days (including the additional day due to the leap year). Thus, the regulatory review period was 4 years and 219 days (1,680 days, including the additional day due to the leap year).

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. U.S. Patent 5,667,767 issued on September 16, 1997. The regulatory review period began on December 14, 2000. Thus, there were no days of regulatory review prior to the issuance of the patent.

Section 156 (c) also sets forth the following exceptions (1)-(3) which may operate to shorten the length of the review period used to calculate the patent term extension:

> (1) each period is reduced by any period during which the application did not act with due diligence.

In the opinion of the Applicant, there has been no lack of due diligence during the period of regulatory review calculated above. Accordingly, no reduction in the review period is required by this provision.

> (2) each period includes only one-half of the number of days in phase (i).

One-half the number of days in phase (i) equals one-half of 818 days (the number of days from December 14, 2000 to March 12, 2003) or 409 days. Adding this number to the number of days in phase (ii) (862 days) results in a review period of 1,271 days.

> (3) if the period remaining in the patent term after the date of approval of the approved product was added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

On the date of approval of the product, 10 years and 6 days remained in the term of U.S. Patent 5,667,767. Adding this period to the review period calculated above yields a period of less than fourteen years. This provision, therefore, does not operate to shorten the period of extension to which U.S. Patent 5,667,767 is entitled.

Section 156(g)(6) limits the period of patent term extension to a maximum of five years from the original date of the patent. The original expiration date of U.S. Patent 5,667,767 is July 27, 2015. The maximum extension allowed by this provision would extend the term to July 27, 2020. Extension of the patent term by the number of days calculated above would not extend the patent beyond July 27, 2020. Accordingly, this provision does not limit the patent term extension available.

In sum, U.S. Patent 5,667,767 is entitled to an extension of patent term until January 18, 2018 or 1,271 days.

13. Applicant acknowledges the duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

14. The fee of $1,120.00 (37 CFR § 1.20(j)) is enclosed herewith.

15. Inquiries and correspondence relating to this Application for Patent Term Extension should be directed to:

Lorna L. Tanner
Foley & Lardner LLP
1530 Page Mill Road
Palo Alto, CA 94304-1125
Tel: 650-856-3700
Fax: 650-856-3710

16. This application is accompanied by two additional copies of the application (for a total of three copies).

17. The undersigned, a duly authorized agent of Micro Therapeutics, Inc., hereby declares:

(1). that she is a patent attorney authorized to practice before the United States Patent and Trademark Office and has general authority from Applicant for the purpose of

transacting all matters reasonably related to obtaining an extension of patent term for U.S. Patent No. 5,667,767;

(2). that she has reviewed and understands the content of this application being submitted pursuant to 35 U.S.C. § 156;

(3). that she believes the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(4). that she believes an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(5). that she believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

Date September 14, 2005

By _____

FOLEY & LARDNER LLP
1530 Page Mill Road
Palo Alto, California 94304-1125
Telephone: (650) 251-1104
Facsimile: (650) 856-3710

Lorna L. Tanner
Attorney for Applicant
Registration No. 50,782

APPENDIX A

US005667767A

United States Patent [19]

Greff et al.

[11] Patent Number: 5,667,767

[45] Date of Patent: Sep. 16, 1997

[54] **COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS**

[75] Inventors: **Richard J. Greff**, Yorba Linda; **Michael L. Jones**, Capistrano Beach; **Scott Evans**, Santa Ana, all of Calif.

[73] Assignee: **Micro Therapeutics, Inc.**, San Clemente, Calif.

[21] Appl. No.: **507,863**

[22] Filed: **Jul. 27, 1995**

[51] **Int. Cl.**[6] **C08J 3/00**; C08K 5/41; C08L 29/04; A61K 31/765

[52] **U.S. Cl.** **424/9.411**; 424/9.4; 424/9.41; 424/78.37; 523/113; 523/105; 523/136; 524/155; 524/173; 524/408; 524/430; 524/439; 524/423; 524/436; 604/20; 604/52; 604/53; 604/56; 604/70

[58] **Field of Search** 424/677, 709, 424/9.4, 9.41, 9.411, 78.37; 523/136, 113, 105; 524/155, 173, 408, 430, 439, 423, 436; 604/20, 52, 53, 56, 70, 21

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,079,124	3/1978	Winchell	424/4
4,631,188	12/1986	Stoy et al.	424/81
4,795,741	1/1989	Leshchiner et al.	514/21
4,938,763	7/1990	Dunn et al.	604/891.1
5,202,352	4/1993	Okada et al.	514/475
5,443,454	8/1995	Tanabe et al.	604/264
B1 4,938,763	7/1995	Dunn et al.	604/891.1

FOREIGN PATENT DOCUMENTS

5-57014	3/1993	Japan .
5-253283	10/1993	Japan .
6-107549	4/1994	Japan .

OTHER PUBLICATIONS

Toxicology, Amdur et al., Editors, *Toxic Effects of Metals*, 4th Edition, pp. 661–664, Pergamon Press, New York, New York.

Guglielmi, et al., *Electrothrombosis of Saccular Aneurysms via Endovascular Approach*, J. Neurosurg., 75:8–14 (1991).

Kinugasa, et al., *Early Treatment of Subarachnoid Hemorrhage After Preventing Rerupture of an Aneurysm*, J. Neurosurg., 83:34–41 (1995).

Kinugasa, et al., *Prophylatic Thrombosis to Prevent New Bleeding and to Delay Aneurysm Surgery*, Neurosurgery, 36(4):661–667 (1995).

Kinugasa, et al., *Direct Thrombosis of a Pseudoaneurysm after Obliteration of a Carotid–Cavernous Fistula with Cellulose Acetate Polymer: Technical Case Report*, Neurosurgery, 35(4):755–760 (1994).

Kinugasa, et al., *Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer, Part II: Preliminary Clinical Experience*, J. Neurosurg., 77:501–507 (1992).

Mandai, et al., *Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer, Part I: Results on Thrombosis in Experimental Aneurysms*, J. Neurosurg., 77:497–500 (1992).

Miyatake, et al., *Cobb's Syndrome and its Treatment with Embolization*, J. Neurosurg., 72:497–499 (1990).

Sadato, et al., *Experimental Study and Clinical Use of Poly(vinyl acetate) Emulsion as Liquid Embolisation Material*, Neuroradiology, 36:634–641 (1994).

Sugiu, et al., *Direct Thrombosis of Experimental Aneurysms with Cellulose Acetate Polymer (CAP): Technical Aspects, Angiographic Follow Up, and Histological Study*, J. Neurosurg., 83:531–538 (1995).

Taki, et al., *A New Liquid Material for Embolization of Arteriovenous Malformatoins*, Am. J. Neuroradiology, 11:163–168 (1990).

Taki, et al., *Selection and Combination of Various Endovascular Techniques in the Treatment of Giant Aneurysms*, J. Neurosurg., 77:37–42 (1992).

Terada, et al., *Embolization of Arteriovenous Malformations with Peripheral Aneurysms using Ethylene Vinyl Alcohol Copolymer*, J. Neurosurg., 75:655–660 (1991).

Yamashita, et al, *Characteristics of Ethylene Vinyl Alcohol Copolymer (EVAL) Mixtures*, Am. J. Neuroradiology, 15:1103–1105 (1994).

Medical Tribune, "Possibility and Limit of Intravascular Surgery", Taki, Oct. 26, 1989, pp. 46–47.

Primary Examiner—Patrick Niland
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis, L.L.P.

[57] **ABSTRACT**

Disclosed are compositions suitable for use in embolizing blood vessels which compositions comprise an ethylene vinyl alcohol copolymer, a biocompatible solvent and a water insoluble contrasting agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate. Also disclosed are methods for embolizing a blood vessel using the compositions described herein.

15 Claims, No Drawings

COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to compositions suitable for use in embolizing blood vessels. In particular, this invention is directed to embolizing compositions comprising an ethylene vinyl alcohol copolymer, a biocompatible solvent and a water insoluble contrasting agent. The compositions of this invention find particular utility in embolizing blood vessels in, for example, the treatment of aneurysms and in ablating diseased tissues.

References

The following publications are cited in this application as superscript numbers: [1]Casarett and Doull's *Toxicology*, Amdur et al., Editors, Pergamon Press, New York, pp. 661–664 (1975) [2]Taki, et al., "A New Liquid Material for Embolization of Arteriovenous Malformations", *American Society of Neuroradiology*, 11: 163–168 (1990) [3]Terada, et al., "Embolization of Arteriovenous Malformations with Peripheral Aneurysms Using Ethylene Vinyl Alcohol Copolymer", *J. Neurosurg.*, 75: 655–660 (1991)

All of the above references are herein incorporated by reference in their entirety to the same extent as if each individual reference was specifically and individually indicated to be incorporated herein by reference in its entirety.

State of the Art

It is desirable in many clinical situations to embolize blood vessels to prevent/control bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.). Embolization of blood vessels has heretofore employed polymer compositions and particulates, e.g., silicone, metallic coils, sclerosing materials and the like. Polymeric materials employed in the polymeric compositions include those which polymerize in situ at the vascular site (e.g., cyanoacrylates) and those wherein a preformed polymer in situ precipitates from a carrier solution at the vascular site.

The in situ polymerization of cyanoacrylates delivered via a catheter causes complications due to premature polymerization and/or adhesion of the polymer to the catheter. Accordingly, there has been recent focus on incorporating preformed polymeric materials into embolization compositions. Ideally, such compositions should be easy to deliver (e.g., low viscosity) and should cause rapid embolization in the intended vascular site. Additionally, these compositions should be sterile, stable, biocompatible and radiopaque. This last property is necessary in order to monitor injection of the embolizing composition into the vascular site and to confirm its presence after the procedure is complete.

Current embolizing compositions employing preformed polymers typically fail to meet one or more of the requirements of ideal embolizing compositions and a compromise must be made in selecting the embolizing agents relative to the given clinical case. At times, embolization of the blood vessel, although called for by the clinical condition of the subject, is not performed due to difficulties in selecting an embolizing composition suitable for use in the given case.

Failure of such embolizing compositions to meet these ideal requirements often arises from the particular combination of embolizing and contrast agents used in the embolizing composition. Specifically, the biocompatible embolizing agent should produce a well defined coherent plug/solid upon contact with blood and the contrast agent should be encapsulated in the formed solid in order to permit adequate definition of the location of embolism formation. While certain compositions comprising an embolizing agent, a contrast agent and a biocompatible solvent such as dimethylsulfoxide (DMSO) have heretofore been disclosed, the choice of embolizing agent in combination with contrast agent is critical to successful use in embolizing conditions. For example, the selected embolizing agent must be biocompatible, capable of rapid precipitation to form a solid, space-filling material and compatible with the selected contrast agent. Additionally, the resulting solid material must be sufficiently coherent so as to minimize fragmentation which results in smaller solid materials being incorporated within the circulation system. As is apparent, the presence of solid materials in the circulation system can lead to embolization of blood vessels at undesired locations. In the extreme, unintended embolization of essential blood vessels can lead to subject death.

The choice of contrast agent relative to the embolizing agent is particularly critical and contrast agents heretofore employed for gastrointestinal tract applications and intravascular injections are not always suitable for use in embolizing blood vessels. For example, while bismuth trioxide is a well known contrast agent, recent evidence indicates that exposure to this agent can lead to progressive mental confusion, irregular myoclonic jerks, a distinctive pattern of disordered gait, and a variable degree of dysarthria which was fatal to subjects who continued its use[1]. Contrast agents which interfere with or retard solid/plug formation for a particular embolizing agent are also not desirable. Moreover, the contrast agent should be water insoluble and must be encapsulated into the resulting precipitate otherwise adverse medical problems can arise. Complications arising from the use of a water insoluble contrast agents which are not encapsulated into the formed precipitate include particles of contrast agent migrating through the circulation system causing embolization of unintended blood vessels. Complications arising from the use of water soluble contrast agents include dissolution of these agents into the blood upon injection into the vascular site leading to potential systemic side effects in the treated subject. Additionally, the use of water soluble contrast agents limits the clinician's ability to continuously monitor the injection of the embolizing agent into the blood vessel because, upon contact with the blood, the contrast agent is dissolved and removed from the site of injection. As still a further complication, the contrast agent selected must not alter the physical properties of the solution, e.g. viscosity, in such a manner as to render the composition unsuitable for vascular use.

In view of the above, whether an embolizing agent and contrast agent will be suitable in combination to embolize a blood vessel is very empirical and substitution of one embolizing agent for another or one contrast agent with another often leads to deleterious results. This problem is not particularly surprising because ultimately a successful combination of embolizing agent and contrast agent requires compatibility between these components in producing the requisite coherent precipitate having the contrast agent encapsulated therein as well as maintaining the requisite properties for vascular use. When, for example, one contrast agent is replaced by another contrast agent, the chemical and physical properties of each contrast agent will dictate whether it is compatible with the selected embolizing agent.

Accordingly, it is not unexpected that contrast agents having different chemical and/or physical properties will result in changes in the overall properties of the embolizing composition.

This invention is directed to our discovery of a novel injectable liquid embolizing composition comprising an ethylene vinyl alcohol copolymer dissolved in a biocompatible solvent and a water insoluble contrast agent selected from either tantalum, tantalum oxide, or barium sulfate. Surprisingly, this embolizing composition is easily delivered to the vascular site and rapidly forms a coherent solid material which readily encapsulates the contrast agent.

Heretofore, Taki, et al.[2] disclose an example of an embolizing composition containing an ethylene vinyl alcohol copolymer (67 mole percent ethylene and 33 mole percent vinyl alcohol) and a water soluble contrast agent (metrizamide) in DMSO. An apparently similar composition was also disclosed by Terada, et al.[3] However, the water soluble contrast agents disclosed in these references significantly limit the suitability of these compositions for use in embolizing blood vessels. Moreover, as above, the apriori substitution of a water insoluble contrast agents for metrizamide is inherently problematic because it is unpredictable what affect the different chemical and/or physical properties of the water insoluble contrast agent as compared to the soluble contrast agent will have on the ultimate properties of the resulting compositions.

SUMMARY OF THE INVENTION

As above, this invention is directed to our discovery of a novel injectable liquid embolizing composition comprising an ethylene vinyl alcohol copolymer dissolved in dimethylsulfoxide or other suitable biocompatible solvent and a water insoluble contrast agent selected from tantalum, tantalum oxide, or barium sulfate.

Accordingly, in one of its composition aspects, this invention is directed to a composition composition comprising:

(a) from about 2.5 to about 8 weight percent of an ethylene vinyl alcohol copolymer embolizing agent;

(b) from about 10 to about 40 weight percent of a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate;

(c) from about 52 to about 87.5 weight percent of a biocompatible solvent

wherein the weight percent of each of the components is based on the total weight of the complete composition.

In one of its method aspects, this invention is directed to a method for embolizing a blood vessel by injecting into said blood vessel a sufficient amount of an embolizing composition comprising:

(a) from about 2.5 to about 8 weight percent of an ethylene vinyl alcohol copolymer embolizing agent;

(b) from about 10 to about 40 weight percent of a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate;

(c) from about 52 to about 87.5 weight percent of a biocompatible solvent

wherein the weight percent of each of the components is based on the total weight of the complete composition

under conditions wherein a precipitate is formed which embolizes the blood vessel.

In a preferred embodiment, the molecular weight of the ethylene vinyl alcohol copolymer composition is selected such that a solution of 6 weight percent of the ethylene vinyl alcohol composition, 35 weight percent of a tantalum contrast agent in DMSO has a viscosity equal to or less than 60 centipoise at 20° C. and more preferably 40 centipoise or less at 20° C. In another preferred embodiment, the ethylene vinyl alcohol copolymer composition comprises from about 25 to about 60 mole percent of ethylene and from about 40 to about 75 mole percent of vinyl alcohol.

Preferably, the biocompatible solvent is dimethylsulfoxide.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to specific embolizing compositions comprising a specific embolizing agent, specific contrast agents and a biocompatible solvent.

Prior to discussing this invention in further detail, the following terms will first be defined:

The term "embolizing" as used in conjunction with "embolizing compositions" and "embolizing agents" refers to a process wherein a material is injected into a blood vessel which thereafter fills or plugs the blood vessel and/or encourages clot formation so that blood flow through the vessel ceases. The embolization of the blood vessel is important in preventing/controlling bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.) by cutting off its blood supply.

The term "ethylene vinyl alcohol copolymers" refers to copolymers comprising residues of both ethylene and vinyl alcohol monomers. Small amounts (e.g., less than 5 mole percent) of additional monomers can be included in the polymer structure or grafted thereon provided such additional monomers do not alter the embolizing properties of the composition. Such additional monomers include, by way of example only, maleic anhydride, styrene, propylene, acrylic acid, vinyl acetate and the like.

Ethylene vinyl alcohol copolymers used herein are either commercially available or can be prepared by art recognized procedures. Preferably, the ethylene vinyl alcohol copolymer composition is selected such that a solution of 6 weight percent of the ethylene vinyl alcohol copolymer, 35 weight percent of a tantalum contrast agent in DMSO has a viscosity equal to or less than 60 centipoise at 20° C. As is apparent to one skilled in the art, with all other factors being equal, copolymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight copolymers. Accordingly, adjustment of the viscosity of the composition as necessary for catheter delivery can be readily achieved by mere adjustment of the molecular weight of the copolymer composition.

As is also apparent, the ratio of ethylene to vinyl alcohol in the copolymer affects the overall hydrophobicity/hydrophilicity of the composition which, in turn, affects the relative water solubility/insolubility of the composition as well as the rate of precipitation of the copolymer in an aqueous solution (e.g., blood). In a particularly preferred embodiment, the copolymers employed herein comprise a mole percent of ethylene of from about 25 to about 60 and a mole percent of vinyl alcohol of from about 40 to about 75. These compositions provide for requisite precipitation rates suitable for use in embolizing blood vessels.

The term "contrast agent" refers to a radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography. The term "water insoluble contrast agent" refers to contrast agents which are essentially insoluble in water (i.e., having a water solubility

of less than 0.01 mg/ml at 20° C.). The water insoluble contrast agents included within the scope of this invention are tantalum, tantalum oxide and barium sulfate, each of which is commercially available in the proper form for in vivo use including a particle size of about 10 μm or less. Other contrast agents suitable for use herein include gold and platinum.

The term "biocompatible solvent" refers to an organic material liquid at least at body temperature of the mammal in which the ethylene vinyl alcohol copolymer is soluble and, in the amounts used, is substantially non-toxic. Suitable biocompatible solvents include, by way of example, dimethylsulfoxide, analogues/homologues of dimethylsulfoxide, and the like. Preferably, the biocompatible solvent is dimethylsulfoxide.

The term "encapsulation" as used relative to the contrast agent being encapsulated in the precipitate is not meant to infer any physical entrapment of the contrast agent within the precipitate much as a capsule encapsulates a medicament. Rather, this term is used to mean that the contrast agent and copolymer form an integral coherent precipitate which does not separate into a copolymer component and a contrast agent component.

Compositions

The compositions of this invention are prepared by conventional methods whereby each of the components is added and the resulting composition mixed together until the overall composition is substantially homogeneous. Specifically, sufficient amounts of the ethylene vinyl alcohol copolymer are added to the biocompatible solvent to achieve the effective concentration for the complete embolizing composition. Preferably, the embolizing composition will comprise from about 2.5 to about 8 weight percent of the ethylene vinyl alcohol copolymer composition based on the total weight of the embolizing composition and more preferably from about 4 to about 5.2 weight percent. If necessary, gentle heating and stirring can be used to effect dissolution of the copolymer into the biocompatible solvent, e.g., 12 hours at 50° C.

Sufficient amounts of the contrast agent are then added to the biocompatible solvent to achieve the effective concentration for the complete embolizing composition. Preferably, the embolizing composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably 35 weight percent. Insofar as the contrast agent is not soluble in the biocompatible solvent, stirring is employed to effect homogeneity of the resulting suspension. In order to enhance formation of the suspension, the particle size of the contrast agent is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm).

The particular order of addition of components to the biocompatible solvent is not critical and stirring of the resulting suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is heat sterilized and then stored preferably in sealed amber bottles or vials until needed.

Methods

The compositions described above are then employed in methods for embolizing mammalian blood vessels. Specifically, a sufficient amount of this composition is introduced into the selected blood vessel by conventional means (e.g., injection or catheter delivery under fluoroscopy) so that upon precipitation of the ethylene vinyl alcohol copolymer, the blood vessel is embolized. The particular amount of embolizing composition employed is dictated by the total volume of the vasculature to be embolized, the concentration of copolymer in the composition, the rate of precipitation (solids formation) of the copolymer, etc. Such factors are well within the skill of the art. The rate of precipitation can be controlled by changing the overall hydrophobicity/hydrophilicity of the copolymer with faster precipitation rates being achieved by a more hydrophobic copolymer composition which, in turn, can be achieved by increasing the ethylene content of the copolymer composition.

One particularly preferred method for delivering the embolizing compositions of this invention to the selected vascular site is via a small diameter medical catheter. The particular catheter employed is not critical provided that polymeric catheter components are compatible with the embolizing composition (i.e., the catheter components will not readily degrade in the embolizing composition). In this regard, it is preferred to use polyethylene in the catheter components because of its inertness in the presence of the embolizing composition described herein. Other materials compatible with the embolizing compositions can be readily determined by the skilled artisan and include, for example, other polyolefins, fluoropolymers (e.g., Teflon™), silicone, etc.

When delivered by catheter, the injection rate dictates, in part, the form of the precipitate at the vascular site. Specifically, low injection rates of approximately 0.05 to 0.3 cc/minute will provide for a precipitate in the form of a kernel or nodule which is particularly beneficial for site specific embolization because the precipitate forms primarily at the point of injection. Contrarily, high injection rates of about 0.1 to 0.5 or more cc/several seconds (e.g., up to ten seconds) will provide for a filament like mass projecting down stream from the catheter tip which is particularly beneficial for providing the embolizing agent deep into the vascular tree. Such procedures are suitable for embolizing tumor masses, organs and arteriovenous malformations (AVM).

When introduced into the vascular site, the biocompatible solvent diffuses rapidly into the blood and a solid precipitate forms which precipitate is the ethylene vinyl alcohol copolymer with the contrast agent encapsulated therein. Without being limited to any theory, it is believed that initially, a soft gel to spongy solid precipitate forms upon contact with the blood which precipitate is open and fibrous in structure. This precipitate then restricts blood flow, entrapping red cells thereby causing clot embolization of the blood vessel.

Utility

The compositions described herein are useful in embolizing mammalian blood vessels which, in turn, can be used to prevent/control bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.). Accordingly, these compositions find use in human and other mammalian subjects requiring embolization of blood vessels.

Additionally, these compositions provide an appropriate vehicle for the delivery of a medicament to the vascular site.

Specifically, a suitable medicament, e.g., a chemotherapeutic agent, growth factor agents, anti-inflammatory agents, anti-spasmatic agents, etc. which are compatible with the embolizing composition can be included in this composition in therapeutic levels and delivered directly to the vascular site.

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples, unless otherwise defined below, the abbreviations employed have their generally accepted meaning:

cc=cubic centimeter

DMSO=dimethylsulfoxide

EVOH=ethylene vinyl alcohol copolymer

gm=gram

mL=milliliters

mm=millimeter

psi=pounds per square inch

Example 1

The purpose of this example is to demonstrate the suitability of ethylene vinyl alcohol copolymer compositions in DMSO as embolizing agents. The tests were conducted by addition of the copolymer solution into saline and determining the precipitation parameters. Rapid formation of a coherent precipitation evidences suitability of the copolymer composition as an embolizing agent.

Specifically, five ethylene vinyl alcohol copolymer resins were employed of varying concentrations—27, 32, 38, 44 and 48 mole percent ethylene (available from EVAL Company of America, Lisle, Ill., USA) having a viscosity grade as defined by a melt index of about 4–15 (gm/10 minutes) at 210° C. The resin appears as clean, translucent cylindrical particles about 1×2 mm. Samples were prepared at 5.2% concentration in DMSO (obtained from Aldrich Chemical Company, Milwaukee, Wis., USA as M8180-2, 99+% purity). Dissolution was complete within 24 hours at 52° C.

Approximately 0.1 to 0.5 mL of each solution was added by needle/syringe to a normal saline solution at 37° C. or at room temperature. All five samples immediately generated a white mass or string of polymer upon contact with saline. As the ethylene content in the sample increased, the resulting precipitate was whiter, tougher and more dense. The two lowest ethylene content resins appeared to yield a weaker, more gelatinous mass, which nevertheless were suitable for use as embolizing agents.

Accordingly, these results indicate that EVOH copolymers are suitable embolizing agents.

Flow rates were assessed for each of these samples at 10 psi and 37° C. over 3 minutes using a 3 French Infusion catheter (available from Micro Therapeutics, Inc., Aliso Viejo, Calif., USA) in order to assess suitability for catheter delivery of these compositions to the vascular site. The results of this analysis are set forth in Table I below:

TABLE I

Ethylene Content in EVOH Copolymer	Flow Rate
27%	0.22 cc/min
32%	0.25 cc/min
38%	0.20 cc/min
44%	0.25 cc/min
48%	0.30 cc/min

The above results indicate that these compositions possess flow rates suitable for catheter delivery to the vascular site. These results also suggest that preferable results are achieved using a more hydrophobic EVOH composition (e.g., about 48 mole % ethylene content) at a concentration of about 2.5 to about 8.0 weight percent.

Example 2

The purpose of this example is to illustrate that not all polymers are suitable as embolizing agents. Specifically, in this example, the EVOH copolymers described above were replaced with polyurethane (DOW PELLETHANE 2363-80A, Dow Chemical Company, Midland, Mich., USA), polymethylmethacrylate (available from Rohm & Haas, Philadelphia, Pa., USA), polycarbonate (MOBAY MAKROLON 2558-1112, Mobay Chemical Company, Bayer Inc., Pittsburgh, Pa., USA), two different cellulose diacetates [Cellulose Acetate NF CA 320-S (~32% acetyl content) and Cellulose Acetate NF CA 398-10 (~39.8 acetyl content) both available from FMC Corp., Pharmaceutical Division, Philadelphia, Pa., USA)] and cellulose triacetate (Cellulose Acetate NF CA 435-75S (~43.5% acetyl content)—FMC Corp., Pharmaceutical Division, Philadelphia, Pa., USA).

The results of this analysis indicated that polyurethane samples were slow to dissolve in DMSO at 52° C. and, upon cooling to room temperature, formed a high viscosity solution/gel unsuitable for injection. In the case of the polymethylmethacrylate, the polymer dissolved in DMSO but the precipitate formed upon addition to saline was unsuitable for use as an embolizing agent because it lacked cohesiveness and easily fragmented. In the case of the polycarbonate, the polymer failed to dissolve in DMSO at 52° C. over 3 days. The cellulose triacetate sample provided too high a viscosity for effective delivery via a catheter at a concentration sufficient to effectively embolize a blood vessel and reduction of the concentration to less than 2.5 weight percent resulted in precipitate formation which was unsuitable for vascular embolization. Only the cellulose diacetates provided suitability for vascular embolization in a manner similar to EVOH and the use of such polymers as embolizing agents is described in further detail in U.S. patent application Ser. No. 08/508,248 filed concurrently herewith as Attorney Docket No. 018413-003 entitled "CELLULOSE DIACETATE COMPOSITIONS FOR USE IN EMBOLIZING BLOOD VESSELS" which application is incorporated herein by reference in its entirety.

Example 3

The purpose of this example is to compare in vitro results achieved by incorporating a water soluble contrast agent and a water insoluble contrast agent of this invention into an embolizing composition containing EVOH in DMSO. Specifically, in this example, an EVOH composition (44 mole percent ethylene) was dissolved into DMSO to provide for an 6.8 weight percent concentration of the copolymer in

DMSO. To this solution was added either tantalum (10 weight percent, available from Leico Industries, New York, N.Y., USA, 99.95% purity, less than 43 μm in size) as a water insoluble contrast agent or metrizamide (38.5 weight percent, available from Aldrich Chemical Company, Milwaukee, Wis., USA) as a water soluble contrast agent. Because these results are in vitro results, the tantalum particle size is not important and the larger particles size is not expected to affect these results.

In the tantalum composition, tantalum settling can result from prolonged standing. Sonification may help but thorough mixing prior to use is required.

Approximately 0.2 mL of the each composition was then added by syringe/needle to a saline solution at 37° C. and the characteristics of the resulting precipitate examined. In the case of the tantalum sample, a precipitate immediately formed which was characterized by firm spongy filaments and nodules. The metrizamide sample on the other hand did not form a well defined solid mass as the metrizamide rapidly diffused away.

Example 4

The purpose of this example is to illustrate that certain embolizing agent/contrast agent combinations provide for physical properties which makes injection of the combination into vascular sites significantly more difficult. Specifically, in this example, a composition comprising 6.8 weight percent of EVOH (44 mole percent ethylene) in DMSO was prepared. The viscosity of this composition was approximately 60 centipoise at 20° C. Upon addition of 38.5 weight percent of metrizamide to this composition, the viscosity increased significantly to approximately 145 centipoise at 20° C.

Contrarily, the addition of 35 weight percent of tantalum or barium sulfate to a similar EVOH/DMSO composition did not materially alter the viscosity of the composition.

The above results indicate that the use of tantalum as the contrast agent provides for compositions with significantly lower viscosity than those employing metrizamide. In turn, such lower viscosities render the compositions easier to deliver either by injection or by catheter to the vascular site thereby proportionally reducing the likelihood of vascular injury.

Example 5

The purpose of this example is to illustrate an in vivo application of the embolizing composition of this invention.

In this example, a 50 pound male hound was prepared for blood vessel embolization using an embolic composition comprising 5.8 weight percent EVOH polymer (containing 48 weight percent ethylene), 20 weight percent tantalum in DMSO was loaded into a syringe. Embolization of the left kidney proceeded by placement of a 3F micro catheter into the kidney through a 5F AngioDynamics Headhunter catheter. The catheter was advanced into the renal artery, flushed with contrast agent to identify the location and then flushed with DMSO, followed by 0.3 cc of the EVOH composition described above, followed yet by more DMSO within the catheter. The EVOH composition was quickly injected into the renal artery. After delivery of about 0.2 cc of EVOH composition, the upper pole of the kidney was blocked. Delivery of the remaining EVOH composition resulted in the entire kidney being embolized.

The above results indicate that the compositions of this invention are suitable for in vivo embolization of blood vessels in mammalian subjects.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

What is claimed is:

1. A composition comprising:
   (a) from about 2.5 to about 8.0 weight percent of an ethylene vinyl alcohol copolymer;
   (b) from about 10 to about 40 weight percent of a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate;
   (c) from about 52 to about 87.5 weight percent of a biocompatible solvent
   wherein the weight percent of each of the components is based on the total weight of the complete composition.

2. The composition according to claim 1 wherein said ethylene vinyl alcohol copolymer comprises from about 25 to about 60 mole percent of ethylene and from about 40 to about 75 mole percent of vinyl alcohol.

3. The composition according to claim 2 wherein said biocompatible solvent is DMSO.

4. The composition according to claim 3 wherein said contrast agent is tantalum.

5. The composition according to claim 3 wherein said contrast agent is tantalum oxide.

6. The composition according to claim 3 wherein said contrast agent is barium sulfate.

7. A method for embolizing a blood vessel by injecting into said blood vessel a sufficient amount of an embolizing composition comprising:
   (a) from about 2.5 to about 8.0 weight percent of an ethylene vinyl alcohol copolymer embolizing agent;
   (b) from about 10 to about 40 weight percent of a water insoluble contrast agent selected from the group consisting of tantalum, tantalum oxide and barium sulfate;
   (c) from about 52 to about 87.5 weight percent of a biocompatible solvent
   wherein the weight percent of each of the components is based on the total weight of the complete composition
   under conditions wherein a precipitate is formed which embolizes the blood vessel.

8. The method according to claim 7 wherein said ethylene vinyl alcohol copolymer comprises from about 25 to about 60 mole percent of ethylene and from about 40 to about 75 mole percent of vinyl alcohol.

9. The method according to claim 8 wherein said biocompatible solvent is DMSO.

10. The method according to claim 9 wherein said contrast agent is tantalum.

11. The method according to claim 9 wherein said contrast agent is tantalum oxide.

12. The method according to claim 9 wherein said contrast agent is barium sulfate.

13. The method according to claim 7 wherein the embolizing composition is injected into the blood vessel at a rate of about 0.05 to 0.3 cc/minute.

14. The method according to claim 7 wherein the embolizing composition is injected into the blood vessel at a rate of at least 0.6 cc/minute.

15. The method according to claim 14 wherein the injection rate of at least 0.6 cc/minute is employed to form a filament like mass projecting down stream from the catheter tip for embolizing tumor masses, organs and arteriovenous malformations (AVM).

* * * * *

APPENDIX B

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 25188

DENNEMEYER & CO.
6990 COLUMBIA GATEWAY DRIVE
SUITE 360
COLUMBIA MD 21046

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,667,767	**$425.00**	**$0.00**	**08/507,863**	**09/16/97**	**07/27/95**	**04**	**NO**	**PAID**	**018413-002**

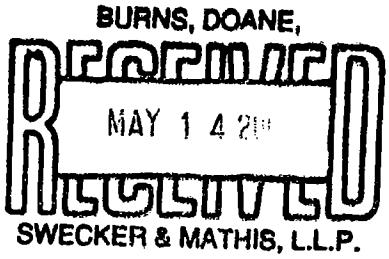
Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Computer Patent Annuities Limited Partnership

PO Box 778, Jersey
JE1 1BL Channel Islands
Phone: +44 (0) 1534 888711
Fax: +44 (0) 1534 888747
E-Mail: cpa@cpajersey.com
Web Site: www.cpajersey.com

Burns Doane, Swecker & Mathis
***
Send all USA Receipts to client.
ALL OTHERS STORE

Our Ref: 2298130/0FRCPT
Your Ref:
Date: 06 APR 2001



Dear Sirs

OFFICIAL RECEIPT / RENEWAL CERTIFICATE

Country Name:	U.S.A.
Type Name:	Small Entity
Patent No.:	5667767
Base date:	16 SEP 1997
Proprietor:	GREFF, RICHARD J.
Client case code:	P12746US0
Reference:	018413-002
Client no.:	0857763

Annuity:	1
Renewal date:	16 MAR 2001

We enclose official confirmation of payment of the annuity indicated above: this document should be kept in a safe place in case proof of payment is required at any time. If you would like such official receipts stored by us in future, rather than sent to you, please let us know by signing and returning this letter: as storage of receipts here is more efficient for us as well as you, this can result in a reduction in charge for future renewals on your account.

Yours faithfully

Computer Patent Annuities Limited Partnership

APPENDIX C

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer Num: 25188

DENNEMEYER & CO.
6990 COLUMBIA GATEWAY DRIVE
SUITE 360
COLUMBIA MD 21046

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,667,767	**$2,300.00**	**$0.00**	**08/507,863**	**09/16/97**	**07/27/95**	**08**	**NO**	**PAID**	**018413-002**

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dennemeyer Patent Renewal Service

Receipts listing dated 23-Mar-2005

for client 2908 Foley & Lardner Silicon Valley
division
cost centre 055 Micro Therapeutics, Inc.

Please find attached hereto the official receipt(s) proving the payment of the annuity/working on the following case(s)

Patent Number	Patentee	Your Reference	Due Date	Tax	Payment Type
US 5667767	Micro Therapeutics, Inc.	355492-1300	16/03/2005	8	Taxes Only

APPENDIX D

Onyx® Liquid Embolic System (LES)

Chronology for Investigational Device Exemption (IDE) G000296

Submissions to FDA by Micro Therapeutics, Inc.				FDA Response References			
Contact Date	**Contact Type/ Reference Number**	**Purpose/Subject**	**Summary Description**	**Contact Date**	**Contact Type Reference Number**	**Purpose/Subject**	**Summary Description**
11-10-00	G000296	Original IDE	Original IDE application submitted.	12-14-00	FDA Response	Original IDE	Conditional approval. Deficiencies to be resolved. **Effective date of IDE**
01-24-01	Supplement S001	12-14-00 FDA letter	Partial response to 12-14-00 letter. Corrections to investigatory plan (FD0841C).	02-28-01	FDA Response	12-14-00 FDA Letter	Conditional approval remains. Deficiencies to be resolved Addressed 12-14-00 deficiencies.
01-30-01	Supplement S001 - Amendment	12-14-00 FDA letter	Amendment to incorporate changes to the labeling and investigational plan described in MTI's response to 12-14-00 letter.	02-28-01	FDA Response	12-14-00 FDA Letter	Conditional approval remains. Deficiencies to be resolved Addressed 12-14-00 deficiencies.
01-30-01	Supplement S002	12-14-00 FDA letter	Partial response to 12-14-00 letter. Corrections to investigatory plan (FD0841C).	02-28-01	FDA Response	12-14-00 FDA Letter	Conditional approval remains. Deficiencies to be resolved
03-12-01	Supplement S003	02-28-01 FDA letter	Partial response to 02-28-01 letter.	04-06-01	FDA Response	02-28-01 FDA letter	Conditional approval remains. Deficiencies to be resolved.
06-26-01	Supplement S004	04-06-01 FDA letter	Response to 04-06-01 letter.	07-27-01	FDA Letter S004	04-06-01 FDA letter	One deficiency to be resolved.
08-07-01	Notification S005	Protocol (Form 7)	Revised National Institutes of Health Stroke Scale (NIHSS) Form 7.	8-10-01	Telephone Contact	Protocol (Form 7)	Verbal acknowledgement. Revised NIHSS Form 7 sent to investigational sites on 08-03-01.
08-31-01	Supplement S006	Labeling (IFU rev)	Instructions for Use (IFU) revisions related to catheter advisory notice; provided copies of U.S. advisory notice.	09-14-01	Telephone Contact	Labeling (IFU rev)	Verbal acknowledgement. Approval of IFU changes.

Onyx® Liquid Embolic System (LES)

Chronology for IDE G000296

Submissions to FDA by Micro Therapeutics, Inc.				FDA Response References			
Contact Date	**Contact Type/ Reference Number**	**Purpose/Subject**	**Summary Description**	**Contact Date**	**Contact Type Reference Number**	**Purpose/Subject**	**Summary Description**
09-05-01	Supplement S007	07-27-01 FDA letter	Partial response consisting of proposed dimethylsulfoxide (DMSO) stability analysis testing.	09-27-01	FDA Response S007	07-27-01 FDA letter	One deficiency to be resolved.
09-06-01	Supplement S008	Protocol	Requested approval to modify core lab procedure for measuring unusual arteriovenous malformations (AVMs).	10-10-01	FDA Response S008	Protocol	Approved to implement.
11-06-01	Supplement S009	DMSO Stability Data	Response to FDA letter of 07-27-01 reporting DMSO stability studies.	12-07-01	FDA Response S009	DMSO Stability Data	Conditional approval pending completion of DMSO stability studies.
12-05-01	Supplement S010	Protocol Deviation	Official notification regarding specific study patient (patient number 29-001).	12-10-01	See 12-10-01 FDA Contact Record	Protocol Deviation	Questions regarding inclusion criteria and analysis and collection of data for specific study patient (patient number 29-001).
12-27-01	Supplement S011	Site Expansion	Request to expand the number of sites.	02-06-02	FDA Response S011	Site Expansion	Request denial; Partial approval of request to expand the number of sites (Reference Supplement request dated 12-27-01).
02-01-02	Annual Report	Annual Report	First Annual Report submitted.	No Response			
02-09-02	Supplement S013	DMSO Stability Studies	DMSO aging/stability studies submitted regarding FDA's conditional approval letter dated 12-07-01.	3-15-02	FDA Response S013	DMSO Stability studies	Deficiencies corrected; unconditional approval for DMSO aging/stability study.
11-14-02	Supplement S014	Patient Count	Request to increase number of patients.	12-06-02	FDA Response S016	Additional Patient Enrollment	Approval to increase number of patients.
03-12-03	Final Report	PMA Application	Submission for IDE Final Report.				
05-21-03	Submission	Continued Access	Continued access after pivotal study, protocol and plan changes, including increased tantalum in Onyx.	06-19-03	FDA Response	Continued Access	Conditional approval for continued access.
02-05-04	Submission	3-5 year Follow-up	Supplement for 3-5 year follow-up pending PMA approval (protocol and informed consent).	02-20-04	FDA Response	3-5 year Follow-up	3-5 year follow-up protocol approved and continued access approval noted.

APPENDIX E

Onyx® Liquid Embolic System (LES)

Chronology for Premarket Approval (PMA) P030004

Submissions to FDA by Micro Therapeutics, Inc. (MTI)				FDA Response References			
Contact Date	**Contact Type/ Reference Number**	**Purpose/ Subject**	**Summary Description**	**Contact Date**	**Contact Type/ Reference Number**	**Purpose/ Subject**	**Summary Description**
03-12-03	**Hardcopy Submission**	**PMA Application**	**MTI submits original PMA Application for Onyx® Liquid Embolic System (LES).**	05-02-03	Hardcopy, FDA to MTI	PMA Application	PMA P030004 - suitable for filing.
05-16-03	A001	PMA Amendment: Pre-clinical data	MTI submits the following: • Component material specifications and test parameters • Sterilization validation summary and references • Onyx® and dimethyl sulfoxide (DMSO) stability test summary and references	05-20-03	A001	PMA Amendment: Pre-clinical data	Acknowledgement of receipt.
06-17-03	A002	PMA Amendment	In response to 05-09-03 facsimile from Peter Hudson (of FDA), MTI submits answers to initial review questions regarding the following: • clinical, statistics, labeling, manufacturing (Mfg.), bioresearch monitoring (BIMO) and pre-clinical	06-19-03	A002	PMA Amendment	Acknowledgement of receipt.
07-9-03	A003	PMA Amendment: Pre-clinical data	MTI submits the following: • Infrared (IR) absorption results • Gel permeation chromatography • Compliance with 0.5 endotoxin (EU)/mL specification • Mfg. procedure for 1 mL syringe • Syringe drawings • High Performance Liquid Chromatography (HPLC) results from Onyx® *in vitro* coil compatibility study • Onyx® 8% solidification time test	07-11-03	A003	PMA Amendment: Pre-clinical data	Acknowledgement of receipt.
07-18-03	A005	PMA Amendment: Pre-cinical data	MTI submits hard copy of the original IR absorption results.	07-23-03	A005	PMA Amendment: Pre-clinical data	Acknowledgement of receipt.

Onyx® Liquid Embolic System (LES)

Chronology for PMA P030004

Submissions to FDA by Micro Therapeutics, Inc. (MTI)				FDA Response References			
Contact Date	**Contact Type/ Reference Number**	**Purpose/ Subject**	**Summary Description**	**Contact Date**	**Contact Type/ Reference Number**	**Purpose/ Subject**	**Summary Description**
07-21-03	A004	PMA Amendment: Pre-clinical data	In response to FDA e-mail request of 07-09-03, MTI submits the following: • Copy of the results of the Onyx® solidification test • Copy of HPLC results	07-22-03	A004	PMA Amendment: Pre-clinical data	Acknowledgement of receipt.
08-12-03	A006	PMA Amendment: Pre-clinical data	MTI submits information regarding Onyx® Material Change • Request for increased tantalum concentration formulation change • Slides submitted regarding in-service training for the increased tantalum arteriovenous malformation (AVM) formulations	08-15-03	A006	PMA Amendment: Pre-clinical data	Acknowledgement of receipt.
08-15-03	A007	PMA Amendment: Clinical data	MTI submits clinical data amendment and statistics with the following: • Frequency of complications • New events since PMA first submitted • Patient cohort tables • Cranial and non cranial tables	08-18-03	A007	PMA Amendment: Clinical data	Acknowledgement of receipt.
03-25-05	A008	PMA Amendment: Integrity hold	Integrity Hold release: • 09-12-03 - Letter placing integrity hold • Independent data audit report provided by Dr. Weiner • Independent data system review provided by Dr. Murphy • 08-24-04 – Corrective Action Plan from MTI submitted • 02-01-05 – BIMO Inspection for corrective action completed	03-28-05	A008	PMA Amendment: Integrity hold	Acknowledgement of receipt.
				07-21-05		**PMA Approval**	**Mail date of Approval of PMA under Section 515**