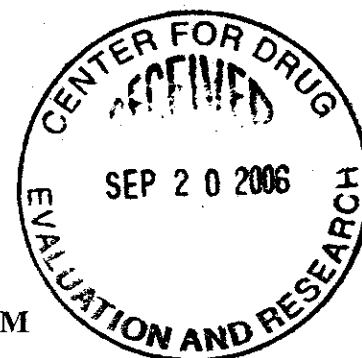


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,820,870)
 Granted: October 13, 1998)
)
 Patentees: Joseph G. Joyce *et al.*)
)
 Assignee: Merck & Co., Inc.)
)
 FOR: RECOMBINANT HUMAN PAPILLOMAVIRUS)
 TYPE 18 VACCINE)

Commissioner for Patents
 U.S. Patent and Trademark Office
Mail Stop Patent Ext.
 Randolph Bldg.
 401 Dulany Street
 Alexandria, VA 22314



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

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), Merck & Co., Inc. (hereinafter referred to as "Applicant") hereby requests an extension of the patent term of United States Patent No. 5,820,870 (hereinafter referred to as "United States Patent 5,820,870" or "the '870 Patent").

Applicant represents that they are the record owners of the entire interest in United States Patent No. 5,820,870, by virtue of assignments from the inventors thereof recorded in the United States Patent and Trademark Office (Reel/Frame: 8908/0930) with respect to the patent application leading thereto as documented in **Exhibit 1** hereto.

The undersigned registered practitioner, Joanne Giesser (Reg. no. 32,838) has been authorized to act on behalf of Applicant with respect to this application, and inquiries and correspondence relating to this application are to be directed as set forth in section (15) below.

2006E-0501

APP1

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 et seq., and follows the numerical sequence and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, which is referred to herein by its proprietary name Gardasil®. Gardasil® is a non-infectious recombinant, quadrivalent vaccine prepared from highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. In addition to VLPs, each vaccine dose contains aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, and water.

Gardasil® has been approved by the Food and Drug Administration for vaccination in females from 9 to 26 years of age for prevention of the following diseases caused by Human Papillomavirus (hereinafter HPV) Types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)
- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

See Approved Label attached as **Exhibit 2** with regard to the statements in this Section (1).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

Gardasil® (Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine) was subject to regulatory review under Section 351 of the Public Health Service Act (42 U.S.C. §262).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

Gardasil® (Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine) received permission for commercial marketing or use under Section 351 of the Public Health Service Act (42 U.S.C. §262) upon approval of BLA, STN BL 125126/0 on June 8, 2006. A copy of the FDA approval letter is attached as **Exhibit 3**.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it 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, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

As active ingredients, a single dose of the approved product contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs.

Neither Gardasil® nor any of the individual active ingredients have been previously approved for commercial marketing or use under the Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted;

Gardasil® was approved on June 8, 2006, and the last day within the sixty day period permitted for submission of an application for patent term extension is August 8, 2006, which is subsequent to the date on which this application has been submitted.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

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

Inventors: Joseph G. Joyce
Hugh A. George
Kathryn J. Hofmann
Kathrin U. Jansen
Michael P. Neeper

U.S. Patent No.: 5,820,870
Earliest Filing Date: March 22, 1995
Grant Date: October 13, 1998
Expiration Date: October 13, 2015

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A full copy of U.S. Patent No. 5,820,870, for which extension is being sought, is attached as **Exhibit 4**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

No Certificate of Correction has been filed and/or issued for U.S. Patent No. 5,820,870.

A copy of the maintenance fee statements, which evidence timely payment of each maintenance fee when due, is attached as **Exhibit 5**.

No disclaimer or reexamination certificate has been filed and/or issued for U.S. Patent No. 5,820,870.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

Claims of U.S. Patent No. 5,820,870 read on the approved product as detailed below.

As described on page 1 of the Approved Label (Exhibit 2), Gardasil® is a non-infectious, recombinant, quadrivalent Human Papillomavirus vaccine that contains highly purified VLPs of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-

defined fermentation media which includes vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type (6, 11, 16, and 18) and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

U.S. Patent 5,820,870 contains claims to purified HPV 18 L1 VLPs comprising recombinant HPV 18 L1 protein having a defined amino acid sequence (SEQ ID NO:2). The specifically defined HPV 18 VLPs are a component of Gardasil®, as evidenced by the inclusion of this defined HPV 18 L1 amino acid sequence in BB IND 9030 (see pages 20-21, Figure 7.9 of BB IND 9030, set forth herein as **Exhibit 6**).

The following is a demonstration of the manner in which specific claims of the '870 patent read on:

(i) **The approved product, if the listed claims include any claim to the approved product;**

Claim	Demonstration
1. Isolated or purified virus-like particles comprising recombinant Human Papillomavirus type 18 L1 protein having the amino acid sequence of SEQ ID No:2.	Gardasil® is a quadrivalent vaccine comprising HPV VLPs of types 6, 11, 16, and 18. The HPV 18 VLP component of Gardasil® comprises HPV 18 L1 protein having the amino acid sequence shown in SEQ ID NO:2 of the '870 patent.
3. The virus-like particles of claim 1, wherein said particles are produced by expression of a recombinant nucleic acid encoding SEQ ID NO:2.	The HPV 18 VLPs in Gardasil® are produced by expression of a recombinant nucleic acid encoding SEQ ID NO:2.
5. A vaccine comprising a pharmaceutically acceptable carrier and an immunoprotective amount of the virus-like particles of claim 1.	Gardasil® comprises (1) an immunoprotective amount of purified VLPs comprising HPV 18 L1 protein having the amino acid of SEQ ID NO:2 of the '870 patent and (2) a pharmaceutically acceptable carrier.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

7. A method of preventing papillomavirus infection in a host comprising administering the vaccine of claim 5 to a host.	Gardasil® is a vaccine comprising (1) an immunoprotective amount of purified VLPs comprising HPV 18 L1 protein having the amino acid of SEQ ID NO:2 of the '870 patent and (2) a pharmaceutically acceptable carrier. Gardasil® is used to prevent papillomavirus infection in a host by its administration to said host.
10. A method of inducing an immune response in an animal comprising administering the virus-like particle claim 1 to the animal.	Gardasil is used to induce an immune response in a human to HPV 6, 11, 16, and 18. Gardasil® comprises HPV 18 L1 protein having the amino acid sequence shown in SEQ ID NO:2 of the '870 patent. Administration of Gardasil to a human induces an immune response in the human.

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

No claims of U.S. Patent No. 5,820,870 are directed toward a method of manufacturing the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The first IND application for the approved product was submitted to the FDA by Merck on April 14, 2000. By letter dated April 19, 2000, the FDA acknowledged receipt of the IND application on April 14, 2000, and assigned IND number BB-IND 9030, resulting in an IND effective date of **May 14, 2000**. A copy of the FDA acknowledgement letter is attached as

Exhibit 7. The title of BB-IND 9030 is “Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18; *S. cerevisiae*) L1 Capsid Virus Like Particle Vaccine with Alum.”

Under these circumstances, the “regulatory review period” under 35 U.S.C. § 156(g)(1) began on **May 14, 2000**, the effective date of BB-IND 9030.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The BLA for Gardasil® was initially submitted to the FDA on December 1, 2005. By letter dated December 12, 2005, the FDA acknowledged receipt of the BLA on December 7, 2005, and assigned Submission Tracking Number (STN): BL 125126, as confirmed by **Exhibit 8**. This establishes **December 7, 2005** as the initial submission date of the BLA for the approved product for purposes of 35 U.S.C. § 156(g)(1).

(C) The date on which the NDA was approved or the Product License issued;

The BLA was approved by the FDA approval letter dated and sent June 8, 2006, setting the effective date of the approval as the June 8, 2006 date of the letter. A copy of this FDA approval letter is attached as **Exhibit 3**. This establishes the end of the “regulatory review period” under 35 U.S.C. 156(g)(1) as **June 8, 2006**.

(11) A brief description beginning on a new page 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;

A listing of the more significant activities undertaken by the marketing applicant with respect to the approved product during the applicable regulatory review period is attached as **Exhibit 9**, the disclosure of which is incorporated herein in its entirety.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

Statement That the Patent Is Eligible For Extension

Applicant is of the opinion that U.S. Patent No. 5,820,870 is eligible for extension under 35 U.S.C. § 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent No. 5,820,870 claims the approved product as detailed in section (9) above.

(2) 35 U.S.C. 156(a)(1)

U.S. Patent No. 5,820,870 was granted on October 13, 1998 on an earliest filed U.S. application filed on March 22, 1995 and there were no terminal disclaimers. As such, the patent expires on October 13, 1998, being 17 years from grant. This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is being submitted by the owners of record of U.S. Patent No. 5,820,870 through an assignment from the inventors as detailed on pages 1-2 above and in **Exhibit 1**, in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the June 8, 2006 approval letter from the FDA (Exhibit 3), Gardasil® was subject to a regulatory review period under Section 351 of the Public Health Service Act (42 U.S.C. § 262) before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of Gardasil® after this regulatory review period is the first permitted commercial marketing of the approved product or any active ingredient thereof, under provision of the Public Health Service Act (42 U.S.C. § 262) under which the regulatory review period occurred, as confirmed by the absence of any approved BLA for the approved product or any active ingredient thereof prior to June 8, 2006.

(7) 35 U.S.C. 156(a)(5)(B)

No other patent has been extended for the same regulatory review period for the product Gardasil®.

Statement Regarding Length of Extension Claimed

The term of U.S. Patent 5,820,870 should be extended 1200 days, from October 13, 2015 to January 25, 2019. In accordance with the implementing regulations of 37 C.F.R. 1.775 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 5,820,870 based on the regulatory review of Gardasil® was determined as follows:

Sec. 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.

(a) If a determination is made pursuant to § 1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (§ 1.321).

U.S. Patent 5,820,870 issued on October 13, 1998 from an earliest filed U.S. application filed on March 22, 1995. Pursuant to 35 U.S.C. 154(c), this patent is entitled to an original term of 17 years from its grant on October 13, 1998, which provides an original expiration date of October 13, 2015.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review

period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of--

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of BB-IND 9030 on May 14, 2000 to the filing (receipt) of STN:BL 125126 on December 7, 2005, being 2033 days.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of STN:BL 125126 on December 7, 2005 to the date of approval of STN:BL 125126 on June 8, 2006, being 183 days.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being 2216 days.

(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

With respect to paragraph (d)(1)(i), **0 (zero) days** of the periods of paragraphs (c)(1) and (c)(2) were before the October 13, 1998 date on which U.S. Patent No. 5,820,870 issued.

With respect to paragraph (d)(1)(ii), 35 U.S.C. 156 (d)(2)(B) provides that if a petition is submitted to the Secretary not later than 180 days after publication of the determination of the applicable regulatory review period, upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall determine if the applicant acted with due diligence during the applicable regulatory review period. The Secretary making this determination shall notify the Director of the determination and shall publish in the Federal register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such request is made within such period, the Secretary shall hold such hearing, and shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, the secretary shall affirm or revise the determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register. There has been no such petition or determination by the Secretary, and thus the number of days under (d)(1)(ii) is **0 (zero) days**.

With respect to paragraph (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph (c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) is one-half of (2033-0-0) days, which is **1016 days** (ignoring the half-day).

Subtracting from the regulatory review period of 2216 days as determined above pursuant to section 1.775(c) the number of days determined above with respect to paragraphs

(d)(1)(i), (ii) and (iii), the term of patent extension is **2216 days minus 0 (zero) days minus 0 (zero) days minus 1016 days** for a sum total of **1200 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 5,820,870 is October 13, 2015 and is not shortened by terminal disclaimer. Adding the 1200 days determined in paragraph (d)(1) to the original term of the patent results in an extended term to **January 25, 2019**.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the June 8, 2006 date of approval of the BLA results in the date **June 8, 2020**.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier of January 25, 2019 and June 8, 2020 is **January 25, 2019**.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The original patent issued after September 24, 1984. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of October 13, 2015 gives a date of **October 13, 2020**. The earlier of January 25, 2019 and October 13, 2020 is **January 25, 2019**.

**(6) If the original patent was issued before September 24, 1984, and
(i) If no request was submitted for an exemption under subsection (i) of
section 505 or subsection (d) of section 507 of the Federal Food, Drug, and
Cosmetic Act before September 24, 1984, by--**

**(A) Adding 5 years to the original expiration date of the patent or earlier
date set by terminal disclaimer; and**

**(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and
(d)(6)(i)(A) of this section with each other and selecting the earlier date; or**

**(ii) If a request was submitted for an exemption under subsection (i) of
section 505 or subsection (d) of section 507 of the Federal Food, Drug, or
Cosmetic Act before September 24, 1984 and the commercial marketing or
use of the product was not approved before September 24, 1984, by--**

**(A) Adding 2 years to the original expiration date of the patent or earlier
date set by terminal disclaimer, and**

**(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and
(d)(6)(ii)(A) of this section with each other and selecting the earlier date.**

Since U.S. Patent 5,820,870 issued after September 24, 1984, no further
adjustments to the extended term of January 25, 2019 is required.

Thus, as calculated above, the term of U.S. Patent No. 5,820,870 is eligible for a
1200 day extension to January 25, 2019.

**(13) A statement that applicant acknowledges a 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 (see § 1.765);**

Applicant acknowledges a duty to disclose to the Patent and Trademark Office
and the Secretary of Health and Human Services any information which is material to any
determination of entitlement to the extension sought.

**(14) The prescribed fee for receiving and acting upon the application for
extension (see § 1.20(j)); and**

As noted in the letter of transmittal submitted with this application, the Patent and
Trademark Office is authorized to charge the filing fee of \$1,120.00 and any additional fees

which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 13-2755.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please address all inquiries and correspondence relating to this application for patent term extension to the following registered practitioner who has been authorized by the assignee to act on its behalf with respect to the filing of this application and all correspondence pertaining thereto:

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Respectfully submitted,

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