Attorney Docket No. 04995.0005-05000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,693,326

Inventors: Andrew Lees, James J. Mond, and Clifford M. Snapper

Assignee: The Henry M. Jackson Foundation for the Advancement of Military Medicine

Title: PRODUCING IMMUNOGENIC CONSTRUCTS USING SOLUBLE CARBOHYDRATES ACTIVATED VIA ORGANIC CYANYLATING REAGENTS

Issue Date: December 2, 1997

REQUEST FOR *INTERIM* EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Mail Stop: **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Commissioner:

Pursuant to 35 U.S.C. § 156(e)(2) and 37 C.F.R. § 1.760, The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. ("Foundation") hereby requests issuance of an interim extension of the term of U.S. Patent No. 5,693,326 ("the '326 patent") for a period of one year from the original expiration date of the patent. The '326 patent will expire on July 29, 2014 and this interim extension application is therefore filed more than three months prior to expiration, in compliance with 37 C.F.R. § 1.760. This is the first request for an interim extension that has been made in this case.

The Foundation calls the attention of the Office to the concurrently-filed application for extension of the patent term of U.S. Patent No. 5,955,079 ("the '079 patent"). Although both the

'326 and '079 applications for patent term extension rely on the same regulatory review period for MENHIBRIX™, the Foundation believes that this should not be a barrier to interim extension of the '326 patent under 35 U.S.C. § 156(d)(5). The limitation in § 156 regarding the extension of one patent per regulatory review period applies only to final extensions under § 156(e)(1) and not interim extensions under § 156(d)(5).

In support of the application for interim extension of the term of the '326 patent, the Foundation notes the following:

1. The Foundation is the assignee of the entire right, title, and interest in the '326 patent. An assignment of the '326 patent from the inventors to the Uniformed Services University of the Health Sciences was recorded with the USPTO at reel 010822, frame 0353, on May 19, 2000, and an assignment from the Uniformed Services University of the Health Sciences to the Foundation was recorded at reel 010822, frame 0375, on May 19, 2000.

2. The marketing applicant for the approved product underlying this application was GlaxoSmithKline Biologicals SA (GSK). GSK has authorized the Foundation to act as their agent for the purpose of seeking this patent term extension. GSK has also licensed the '326 patent from the Foundation.

3. A letter dated March 4, 2013, from the U.S. Food and Drug Administration (of record) indicates that MENHIBRIX™ was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4), and that the approval of the Biologics License Application (BLA) for MENHIBRIX™ represented the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1). The letter from FDA also indicated that the application for extension of the patent term of the '326 patent was timely filed within 60 days from the approval of the BLA for MENHIBRIX™.

This interim request is being submitted more than three months prior to patent expiration, and has been filed electronically. M.P.E.P. § 2755. For ease of reference, the following information is structured to correspond to the sections of 37 C.F.R. § 1.740, as directed in 37 C.F.R. § 1.790(b).

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

The approved vaccine will be marketed under the trademark MENHIBRIX™ and contains three polysaccharide-protein conjugate components — *Neisseria meningitidis* serogroup C capsular polysaccharide (PSC), *Neisseria meningitidis* serogroup Y capsular polysaccharide (PSY), and *Haemophilus influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), each covalently bound to tetanus toxoid (TT) using 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP). The vaccine is formulated as a lyophilized product that is reconstituted prior to intramuscular injection using a liquid saline diluent. The reconstituted product contains 2.5 µg of PRP-TT, 5 µg PSC-TT and 5 µg PSY-TT per 0.5 mL dose volume. A copy of the approved package insert for MENHIBRIX ™ was previously attached as Exhibit D to the initial application for patent term extension.

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

The regulatory review for MENHIBRIX ™ occurred under Section 351 of the Public Health Service Act (PHSA), which is codified at 42 U.S.C. § 262. Section 351 (42 U.S.C. § 262) provides for the submission and approval of a Biologics License Application (BLA).

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

MENHIBRIX™ received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to Section 351 of the PHSA (42 U.S.C. § 262) on June 14, 2012. A copy of the letter from the FDA approving the marketing of MENHIBRIX™ was previously attached as Exhibit E to the initial application for patent term extension.

(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.

The approved vaccine contains three active ingredients: PSC-TT, PSY-TT, and PRP-TT. This combination was not 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 prior to the approval of MENHIBRIX™ on June 14, 2012.

(5) A complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue, and the date of expiration.

Inventors: Andrew Lees, James J. Mond, and Clifford M. Snapper

Patent No.: 5,693,326

Issue Date: December 2, 1997

Expiration Date: July 29, 2014

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

A copy of the '326 patent was previously submitted as Exhibit A to the initial application for patent term extension.

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

A terminal disclaimer has been filed for this patent, disclaiming the portion of the '326 patent that extends beyond the expiration date of U.S. Patent No. 5,651,971. A certificate of correction has also been filed, as well as a certificate for correction of inventorship under 35 U.S.C. § 256 adding James J. Mond and Clifford Snapper as inventors. The 3½, 7½, and 11½ year maintenance fees for the '326 patent have been timely paid.

A copy of the terminal disclaimer, certificate of correction, certificate for correction of inventorship, and receipt showing payment of the maintenance fees was previously attached as Exhibit F to the initial application for patent term extension.

(8) 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:

- **(i) The approved product, if the listed claims include any claim to the approved product;**
- **(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**
- **(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

The '326 patent claims methods of preparing and using the conjugates in the approved product, MENHIBRIX™. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product.

> 1. In a method for preparing a vaccine comprising an immunogenic construct and a pharmaceutically acceptable carrier, the improvement comprising producing the immunogenic construct by a process comprising:
>
> (a) activating a viral, fungal or bacterial polysaccharide with an organic cyanylating reagent selected from the group consisting of 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate, N-cyanotriethyl-ammonium tetrafluoroborate, and p-nitrophenylcyanate, to form an activated carbohydrate; and
>
> (b) coupling said activated carbohydrate directly or indirectly to a protein to form the immunogenic construct capable of stimulating an immune response.

The approved product contains bacterial polysaccharides (PSC, PSY, and PRP), each of which is conjugated to a protein (TT) by activating the bacterial polysaccharides with 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate (CDAP). *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 2. A method according to claim 1, wherein said organic cyanylating reagent is 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate..

The conjugates in the approved product are prepared using CDAP.

> 3. A method according to claim 2, wherein said polysaccharide and said protein are soluble in water.

The conjugates in the approved product are dissolved and administered in sterile saline solution. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 8. A method according to claim 1, wherein the polysaccharide is selected from the group consisting of dextran, Pneumococcal polysaccharide, Haemophilus influenzae polysaccharide, Group A streptococcus polysaccharide, Group B streptococcus polysaccharide, and N. meningitidis polysaccharide.

The conjugates in the approved product are *Neisseria meningitidis* serogroup C capsular polysaccharide, *Neisseria meningitidis* serogroup Y capsular polysaccharide, and *Haemophilus*

influenzae type b capsular polysaccharide. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 9. A method according to claim 1, wherein the polysaccharide is a water-soluble viral or bacterial polysaccharide.

The conjugates in the approved product are dissolved and administered in sterile saline solution. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 10. A method according to claim 1, wherein the protein is a water-soluble protein.

The conjugates in the approved product are dissolved and administered in sterile saline solution. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 11. A method according to claim 1, wherein the protein is selected from the group consisting of bovine serum albumin, pertussis toxoid, tetanus toxoid, malaria-derived peptide, an antibody, a toxoid, and a lipoprotein.

The conjugates in the approved product each comprise tetanus toxoid. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 13. A method for producing an immune response in a patient comprising:
>
> (a) preparing a vaccine comprising an immunogenic construct capable of stimulating an immune response and a pharmaceutically acceptable carrier, wherein the immunogenic construct is produced by; (i) activating a viral, fungal or bacterial polysaccharide with an organic cyanylating reagent selected from the group consisting of 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate, N-cyanotriethyl-ammonium tetrafluoroborate, and p-nitrophenylcyanate, to form an activated carbohydrate, and (ii) covalently joining said activated carbohydrate to a protein to form the immunogenic construct; and
>
> (b) administering the vaccine to said patient.

The approved product is administered to a patient to induce an immune response, and the conjugates in the approved product comprise bacterial polysaccharides (PSC, PSY, and PRP), each of which is conjugated to a protein (TT) by activating the bacterial polysaccharides with 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate (CDAP). *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 14. A method according to claim 13, wherein said organic cyanylating reagent is 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate.

The conjugates in the approved product are prepared using CDAP.

> 16. A method according to claim 14, wherein the protein is a water-soluble protein.

The conjugates in the approved product are dissolved and administered in sterile saline solution. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 17. A method according to claim 14, wherein the polysaccharide is selected from the group consisting of dextran, Pneumococcal polysaccharide, Haemophilus influenzae polysaccharide, Group A streptococcus polysaccharide, Group B streptococcus polysaccharide, and N. meningitidis polysaccharide.

The conjugates in the approved are *Neisseria meningitidis* serogroup C capsular polysaccharide, *Neisseria meningitidis* serogroup Y capsular polysaccharide, and *Haemophilus influenzae* type b capsular polysaccharide. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

> 18. A method according to claim 14, wherein the protein is selected from the group consisting of bovine serum albumin, pertussis toxoid, tetanus toxoid, malaria-derived peptide, an antibody, a toxoid, and a lipoprotein.

The conjugates in the approved product each comprise tetanus toxoid. *See* Exhibit D of the initial application for patent term extension (Approved Package Insert).

(9) 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;

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

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

GlaxoSmithKline Biologicals SA (GSK), the marketing applicant, filed an IND application on May 12, 2004 (Exhibit G of the initial application for patent term extension). The IND application for MENHIBRIX™ was assigned BB-IND No. 11,706. The IND became effective on June 12, 2004, thirty days after the FDA received the IND request from GSK. *See* 21 U.S.C. § 355(i)(2).

The Biologics License Application (BLA) for MENHIBRIX™, BL 125363, was submitted to the FDA on August 12, 2009 (Exhibit I of the initial application for patent term extension).

BL 125363 was approved by the FDA on June 14, 2012 (Exhibit E of the initial application for patent term extension).

(10) 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.

Discussions between GSK and FDA were ongoing throughout the regulatory period. GSK initiated discussions with FDA during a pre-IND meeting on April 9, 2003, and also conducted a pre-Phase 3 teleconference with FDA on June 8, 2005 and a pre-BLA meeting on June 19, 2009.

On May 12, 2004, GSK submitted an IND application for MENHIBRIX™ (Exhibit G of the initial application for patent term extension). The IND (No. 11,706) became effective on June 12, 2004 (Exhibit H of the initial application for patent term extension). MENHIBRIX™ was designated as a Fast Track Development program on January 24, 2005.

The first Phase II trial in the U.S. of MENHIBRIX™ was initiated on August 13, 2004 and completed on March 29, 2006. Subsequent Phase II studies were conducted. The results of the phase II studies were supportive of further development, and the first Phase III study was initiated on February 22, 2006.

GSK continued to communicate with FDA during the regulatory period, including providing FDA with notifications of Protocol Amendments and amendments to the Chemistry, Manufacturing and Control, Immunogenicity, and Statistical Analysis Sections of the IND. GSK also consulted with FDA regarding additional studies evaluating the effects of co-administering MENHIBRIX™ with other pediatric vaccines. Further detail regarding important communications and other activities undertaken by GSK during the regulatory period are shown in the chronology of major regulatory review events for MENHIBRIX™ (Exhibit J of the initial application for patent term extension).

On August 12, 2009, GSK submitted a BLA for MENHIBRIX™, which was assigned BLA number BL 125363 (Exhibit I of the initial application for patent term extension). On September 23, 2011, GSK received a Complete Response letter from FDA indicating that the agency's review of the MENHIBRIX™ file was complete and that questions remained to be answered prior to approval. GSK worked with FDA to provide responsive information and the BLA was approved on June 14, 2012 (Exhibit E of the initial application for patent term extension). Exhibit J of the initial application for patent term extension provides a chronology of major regulatory review events for MENHIBRIX™.

(11) 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 the extension claimed, including how the length of the extension was determined.

It is the opinion of the Applicant that the '326 patent is eligible for patent term extension under 35 U.S.C. § 156(a). The Applicant claims an extension of 1825 days.

Statement of Eligibility of the Patent for Extension

Under 35 U.S.C. § 156(a)

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 (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d)(1)-(4); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§ 156(a)(5)(B) and 156(a)(5)(C), the 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.

Each of these elements is satisfied here:

(1) The initial application for patent term extension, and this interim extension application, have been submitted before expiration of the patent term.

(2) The term of the '326 patent has never been extended under 35 U.S.C. § 156(e)(1).

(3) This application is submitted by Anthony C. Tridico, an attorney for the law firm Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, which has been appointed under a power of attorney to act for the owner of the '326 patent for the purpose of

filing this Request (Exhibit C of the initial application for patent term extension). The initial application was submitted in accordance with 35 U.S.C. § 156(d) within the sixty-day period beginning June 14, 2012, when the product received permission for marketing under the PHSA and contains the information required under 35 U.S.C. §§ 156(d)(1)(A)-(E).

(4) The product was the subject of BB-IND No. 11,706 (filed on May 12, 2004; effective on June 12, 2004), and BLA 125363 (filed on August 12, 2009 and approved on June 14, 2012). Thus, the product was subject to a regulatory review period under § 351 of the PHSA before its commercial marketing or use.

(5) Finally, the permission for commercial marketing of the approved product after regulatory review under PHSA § 351 is the first permitted commercial marketing of the approved product in the United States. This is confirmed by the absence of any approved BLA under which the approved product could be commercially marketed prior to June 14, 2012.

Statement as to the Length of the Extension Claimed

In Accordance with 37 C.F.R. 1.775

The term of the '326 patent should be extended by 1825 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

(1)	1887	The number of days in the period beginning on the effective date of the IND (June 12, 2004) and ending on the date the BLA was initially submitted (August 12, 2009). This is the "testing phase" as defined in 37 C.F.R. § 1.775(c)(1).
(2)	1037	The number of days in the period beginning on the date the BLA was initially submitted (August 12, 2009) and ending on the date of BLA approval (June 14, 2012). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2).
(3)	2924	The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. § 1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '326 patent. 37

		C.F.R. § 1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. § 1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2924	The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii).
(8)	0	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '326 patent. 37 C.F.R. § 1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. § 1.775(d)(1)(ii).
(10)	0	The sum of (8) and (9).
(11)	2924	The difference between the regulatory review period (7) and (10).
(12)	1887	The number of days of the testing phase (1).
(13)	0	The number of days from (10).
(14)	1887	Subtract line (13) from line (12).
(15)	943	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1]
(16)	1981	Subtract line (15) from line (11).
(17)	July 29, 2014	The original expiration date of the '326 patent.
(18)	January 1, 2020	The expiration date of the '326 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2)
(19)	June 14, 2012	The date of approval of the application under § 351 of the PHSA.
(20)	14 years	The limitation of 37 C.F.R. § 1.775(d)(3).
(21)	June 14, 2026	The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3).
(22)	January 1, 2020	The earlier of line (18) or line (21)
(23)	July 29, 2014	The original expiration date of the '326 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. § 1.775(d)(5)
(25)	July 29, 2019	The number of years on (24) plus the date on (23).

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

(26)	July 29, 2019	The earlier of line (22) or line (25)
(27)	July 29, 2014	The original expiration date of the '326 patent
(28)	1825	The number of days which is the difference between the date on line (27) and the date on line (26)

(12) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to 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.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '326 patent by this Request as required by 37 C.F.R. § 1.765.

(13) Prescribed Fee:

Please charge any required fees to Deposit Account No. 06-0916. The Commissioner is also authorized to charge any additional fees to Deposit Account No. 06-0916.

(14) 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

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In view of the foregoing, the Foundation requests that the Commissioner grant an *interim* extension of one year to U.S. Patent No. 5,693,326, and also reiterates the original request for extension of the patent term by a total of 1825 days under 35 U.S.C. § 156.

The undersigned, an attorney of the law firm Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, submits that he is a patent attorney duly authorized to practice before the United States Patent and Trademark Office (Reg. No. 45,958) and has reviewed and understands the contents of this application submitted pursuant to 35 U.S.C. § 156. The undersigned has power of attorney from the Foundation for the purpose of transacting all matters relating to U.S. Patent No. 5,693,326, including this interim application for patent term extension. A copy of the Power of Attorney from the Foundation to the undersigned was submitted with the original application for patent term extension as Exhibit C.

Favorable action is earnestly solicited. In the event that a fee is due, please charge our Deposit Account No. 06-0916.

Respectfully submitted,

Dated: 10 March 2014

/Anthony C. Tridico/
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