PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: **5,101,013**

Filed: **August 9, 1988**

Issued: **March 31, 1992**

Title: **Process for Isolating Basic Proteins from Protein Mixtures**

Inventors: **Michael Dörschug; Ranier Obermeier**

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on

6-16-2000
Date of Deposit

Debra L. Wetherill
Signature

EL620187059US
Express Mail Certificate

DECLARATION OF PATENT OWNER

Assistant Commissioner for Patents
Washington, D.C. 20231
Sir:

Stephen L. Nesbitt, authorized patent attorney for the Applicant, Hoechst AG; submits this declaration as required by 37 C.F.R. § 1.740, along with an Application for Extension of Patent Term for U.S. Patent No. 5,101,013, and hereby declares THAT:

(1) I am a patent attorney authorized to practice before the U.S. Patent and Trademark Office and have general authority from the owner of U.S. Patent No. 5,101,013 to act on its behalf in regard to patent matters;

(2) I have reviewed and understand the contents of the enclosed Application for Extension of Patent Term for U.S. Patent No. 5,101,013.

(3) I believe that U.S. Patent No. 5,101,013 is subject to an Extension of Patent Term pursuant to 37 C.F.R. § 1.710;

(4) I believe a Patent Term Extension of 976 days for U.S. Patent No. 5,101,013 is justified under 35 U.S.C. § 156 and the applicable regulations related thereto;

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(5) I believe that U.S. Patent No. 5,101,013 meets the conditions for extension of term as set forth in 37 C.F.R. § 1.720; and

(6) all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code § 1001, and that such willful false statements may jeopardize the validity of the application for extension or any patent extended thereon.

Respectfully submitted,

Stephen L. Nesbitt, Reg. No. 28,981
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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JUN 16 2000
PATENT & TRADEMARK OFFICE

In re U.S. Patent No.: **5,101,013**

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

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

Hoechst Aktiengesellschaft as the owner of record of U.S. Patent No. 5,101,013, hereby submits this application for Extension of Patent Term pursuant to 35. U.S.C. § 156. The Applicant requests that the term of U.S. Patent No. 5,101,013 be extended for 976 days in accordance with 35 U.S.C. § 156 and that this extended term be added to the unextended expiration date of March 31, 2009 in accordance with applicable U.S. law so as to expire on December 2, 2011.

OWNER OF RECORD

Hoechst Aktiengesellschaft, Frankfurt/Main, Germany is the original assignee of U.S. Patent No. 5,101,013, the subject of the instant Application for Extension of Patent Term, as evidenced by the attached Notice of Recordation and recorded Assignment, **Appendix A**.

The numbered sections below correspond to the specific requirements for an Application for Extension of Patent Term as set forth in 37 C.F.R. § 1.740(a) (1)-(17).

(1) IDENTIFICATION OF THE APPROVED PRODUCT

The Drug Product which is the subject of the instant Application for Extension of Patent Term is Gly(A21), Arg(B31), Arg(B32) human insulin, the active ingredient of Lantus® (Insulin glargine [rDNA origin], (5 mL and 10mL vials and 3mL cartridges). Lantus has the following amino acid sequence:

-S-S-

H_2N-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Gly-COOH

-S-S- -S-S-

H_2N-Phe-Val-Asn-Gln-His-Leu-Cys-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-

HOOC-Arg -Arg-Thr-Lys Pro-Thr-Tyr-Phe-Phe-Gly-

Lantus is indicated for once daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for control of hyperglycemia as shown in the prescribing information approved by the FDA for Lantus®, **Appendix B**.

(2) IDENTIFICATION OF FEDERAL STATUTE

Pursuant to 21 U.S.C. § 355(a), "[N]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug".

As a new drug product for human use, insulin glargine [rDNA origin] was subjected to regulatory review by the U.S. Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(b)(1) which is also cited as Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. Thus, regulatory review and approval by the FDA was required for marketing insulin glargine [rDNA origin] in the U.S. Pursuant to this statute, insulin glargine [rDNA origin] was the subject of a New Drug Application (NDA 21-081) for which numerous clinical trials were conducted under an Investigational New Drug (IND) filing.

(3) IDENTIFICATION OF DATE OF APPROVAL UNDER FEDERAL STATUTE

By letter of April 20, 2000, attached as **Appendix C**, FDA issued to Aventis Pharmaceuticals Inc., an approval for marketing Lantus® (5 mL and 10mL vials and 3mL cartridges). FDA concluded that,

based upon review of the NDA, "adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. " Page 1 of 3 Letter from FDA to Aventis Pharmaceuticals Inc., **Appendix C**.

(4) IDENTIFICATION OF ACTIVE INGREDIENT

The active ingredient in Lantus® for which regulatory approval was obtained from FDA is insulin glargine [rDNA origin] or Gly(A21), Arg(B31), Arg(B32) human insulin, as indicated by the Prescribing Information approved by FDA for Lantus® attached in **Appendix B**.

The drug product insulin glargine [rDNA origin], including any salt or ester thereof, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act either as a single entity or in combination with any other active ingredient.

(5) STATEMENT AS TO 60 DAY WINDOW

The instant Application for Extension of Patent Term of U.S. Patent No. 5,101,013 for insulin glargine [rDNA origin] has been submitted within the 60 day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day for submission of the instant Application is 60 days from April 20, 2000 or June 19, 2000.

(6) IDENTIFICATION OF PATENT

The instant Application relates to the following Patent:

U.S. Patent No. 5,101,013
Inventors: Michael Dörshug and Ranier Obermeier
Date Issued: March 31, 1992
Expiration Date: March 31, 2009

(7) COPY OF PATENT

A copy of U.S. Patent No. 5,101,013 is attached in **Appendix D**.

(8) COPY OF DISCLAIMER, CERTIFICATE OF CORRECTION, ETC.

With respect to U.S. Patent No. 5,101,013, which is the subject of the instant application, no disclaimer or reexamination certificate has been issued or filed. A certificate of correction dated July 20, 1993 is included in Appendix D. All Maintenance fee payments due have been paid.

(9) STATEMENT REGARDING PATENT CLAIMS AND SHOWING

The Patent which is the subject of the instant Application for Extension of Patent Term (U.S. Patent No, 5,101,013) claims the a process for the isolation of the approved product insulin glargine [rDNA origin]. The applicable claims are Claim 1-13.

The following analysis identifies the applicable claims of U.S. Patent No. 5,101,013 and demonstrates the manner in which each applicable claim reads on the approved product or approved method of use:

Claim 1 reads as follows:

1. A process for the isolation of basic proteins from a protein mixture containing said basic proteins obtained by enzymatic cleavage of proinsulin, or a natural, semi-synthetic, or genetically engineered derivative thereof consisting essentially of

loading a strongly acid cation exchanger with the protein mixture; and

eluting said proteins by means of a water and C_1-C_4-alkanol mixture of about 10 to about 50% by volume of alkanol, wherein the pH of the elution solution is about 2.5 to about 5.5.

Claim 1 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 2 reads as follows:

2. The process as claimed in claim 1, wherein the strong acid cation exchanger employed contains sulfo groups.

Claim 2 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 3 reads as follows:

3. The process as claimed in claim 1, wherein the loading of the strongly acid cation exchanger is carried out at a pH between about 3.5 to about 4.0.

Claim 3 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 4 reads as follows:

4. The process as claimed in claim 1, wherein the mixture of water and C_1-C_4-alkanol employed for the elution contains ethanol or isopropanol as the C_1-C_4-alkanol.

Claim 4 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 5 reads as follows:

5. The process as claimed in claim 1, wherein the loading elution solution also contains a buffer.

Claim 5 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 6 reads as follows:

6. The process as claimed in claim 1, wherein the elution is carried out with an ammonium or alkali metal salt gradient of between about 0 to about 1 mol/l.

Claim 6 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 7 reads as follows:

7. The process as claimed in claim 1 wherein the water and C_1-C_4-alkanol mixture contains about 20 to 40% by volume of alkanol.

Claim 7 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 8 reads as follows:

8. The process as claimed in claim 7, wherein the water and C_1-C_4-alkanol mixture contains about 30% by volume of alkanol.

Claim 8 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 9 reads as follows:

9. The process as claimed in claim 2, where the strongly acid cation exchanger employed contains sulfopropyl groups.

Claim 9 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 10 reads as follows:

10. The process as claimed in claim 4, wherein the water and alkanol mixture used for the elution contains isopropanol as the alkanol.

Claim 10 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 11 reads as follows:

11. The process as claimed in claim 5, wherein the buffer is an organic acid.

Claim 11 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 12 reads as follows:

12. The process as claimed in claim 11, wherein the organic acid is lactic acid.

Claim 12 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

Claim 13 reads as follows:

13. The process as claimed in claim 6, wherein the elution is carried out with an ammonium or alkali metal salt gradient of between about 0.15 to 0.35 mol/l.

Claim 13 is a method of manufacturing insulin glargine [rDNA origin] by isolation from a mixture of proteins.

(10) STATEMENT OF REGARDING RELEVANT DATES

The following are relevant dates and information for a determination of the applicable regulatory review period pursuant to 35 U.S.C. § 156:

a. IND Number and Effective date:
Insulin glargine [rDNA origin] is the subject of IND No. 49,078 which was submitted on November 10, 1995 and received by FDA on November 14, 1995 as evidenced by the FDA Acknowledgement Letter attached hereto as **Appendix E**. The IND became effective 30 days after receipt by FDA pursuant to 21 C.F.R. § 312.40(b)(1) or on December 14, 1995.

b. NDA Number and Initial Submission Date:

Insulin glargine [rDNA origin] is the subject of NDA 21-081 which was initially submitted to FDA on April 23, 1999 as evidenced by the Letter to FDA Accompanying the NDA Submission attached hereto as **Appendix F**.

c. NDA Approval Date:

NDA 21-081 was approved by FDA on April 20, 2000 as evidenced by the FDA Approval Letter attached hereto as **Appendix C**.

(11) DESCRIPTION OF SIGNIFICANT ACTIVITIES DURING REGULATORY REVIEW PERIOD

a. Significant Activities During IND Period:

During the IND Period from December 14, 1995 to April 23, 1999, Applicant conducted extensive clinical trials both in the U.S. and in Foreign countries in over 4200 patients designed to demonstrate the safety and efficacy of insulin glargine [rDNA origin] in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for control of hyperglycemia. A brief summary of various clinical trials including the clinical pharmacokinetic studies conducted with the approved drug product (Lantus®, insulin glargine [rDNA origin] tablets, 10 mg, 20 mg, 100 mg) together with applicable start and completion dates and a brief description of these studies is attached hereto as Table of Clinical Trials in **Appendix G**. In addition to these activities, various other activities were also conducted during this time period including, for example, manufacturing regulatory compliance, various non-clinical studies designed to support safety and efficacy, and the like.

b. Significant Activities During the NDA Period:

During the NDA Period from April 23, 1999 to April 20, 2000, Applicant corresponded extensively with the FDA concerning follow-up activities and questions or requests by FDA concerning the NDA. In addition to these activities, various other activities were also conducted during this time period including, for example, safety update reports, annual summary for the NDA, and the like. A brief description of some of the significant communications with FDA concerning the drug product insulin glargine [rDNA origin] during this period is attached hereto as a Chronological Listing of Significant Communications in **Appendix H**.

(12) STATEMENT OF ELIGIBILITY, LENGTH OF EXTENSION AND METHOD OF DETERMINATION

In the opinion of Applicant, U.S. Patent No. 5,101,013 (the '013 patent) is eligible for a Patent Term Extension pursuant to 35 U.S.C. § 156(a) for the following reasons:

(1) the '013 patent claims a process for the isolation of the drug product insulin glargine [rDNA origin];

(2) the term of the '013 patent has not expired prior to the submission of the instant Application for Extension of Term;

(3) the term of the '013 patent has never been extended under 35 U.S.C. § 156;

(4) the instant Application for Extension of Patent Term has been submitted in accordance with 35 U.S.C. § 156(d)(1) through (4);

(5) the drug product insulin glargine [rDNA origin], which is the active ingredient of Lantus®, was subject to regulatory review pursuant to 21 U.S.C. § 355(b)(1) prior to its approval by FDA for commercial marketing on April 20, 2000;

(6) the FDA approval for commercial marketing on April 20, 2000 was the first permitted commercial marketing or use of the drug product insulin glargine [rDNA origin], including any salt or ester thereof as a single entity or in combination with another active ingredient, under 21 U.S.C. § 355.

Applicant believes that the proper length of the Patent Term Extension for U.S. Patent No. 5,101,013 pursuant to 35 U.S.C. § 156 due to the regulatory review period for the drug product insulin glargine [rDNA origin] is 976 days which, when added to the expiration date of the patent, would extend the expiration date of U.S. Patent No. 5,101,013 to December 2, 2011.

The Patent Term Extension was calculated pursuant to 37 C.F.R. § 1.775 as follows:

a. The Regulatory Review Period was calculated as the sum of the IND period and the NDA period as follows:

> The IND period began on the date the IND became effective (30 days after receipt of the IND by FDA). Receipt of the IND was on November 14, 1995 and the effective date of the IND was therefore 30 days later on December 14, 1995. The IND period ended on the date the NDA was submitted to FDA on April 23, 1999. The time period from December 14, 1995 to April 23, 1999 is 1226 days.
>
> The NDA period began on the date the NDA was submitted to FDA on April 23, 1999 and ended on the date the FDA approved the NDA on April 20, 2000. The time period from April 23, 1999 to April 20, 2000 is 363 days.
>
> The Regulatory Review Period is the sum of the IND period (1226 days) and the NDA period (363 days). Therefore, the Regulatory Review Period is 1589 days.

b. The Patent Term Extension Period was calculated by adjusting the Regulatory Review Period as follows:

> (i) subtracting the number of days within the Regulatory Review Period which were on and before the date on which the patent issued: Since the '013 patent issued on March 31, 1992, no days within the

Regulatory Review Period are on or before the date on the patent issued. Therefore, 0 days were subtracted.

(ii) subtracting the number of days within the Regulatory Review Period during which Applicant did not act with due diligence: Applicant believes that due diligence was pursued during the entire Regulatory Review Period. Therefore, 0 days were subtracted.

(iii) subtracting one-half the number of days in the IND period from the Regulatory Review Period: Once-half of the IND Period of 1226 days is 613 days. This is subtracted from the Regulatory Review Period of 1589 days to yield 976 days as the applicable Patent Term Extension Period.

c. The Extended Term Expiration date of U.S. Patent No. 5,101,013 is calculated as follows:

The Patent Term Extension Period of 976 days is added to the expiration date of March 31, 2009 in accordance with applicable U.S. law to give an Extended Term Expiration Date of December 2, 2011.

d. The 14 Year Cap Date is calculated as follows:

14 years was added to the date of NDA approval on April 20, 2000 to yield a 14 Year Cap Date of April 20, 2014.

e. The 5 Year Cap Date is calculated as follows:

Since the '013 patent was issued subsequent to 24 September 1984, 5 years is added to the expiration date of the patent (March 31, 2009) to yield a 5 Year Cap Date of March 31, 2014.

f. Patent Term Extension Expiration Date for U.S. Patent No. 5,101,013 is calculated as follows:

Since the Extended Term Expiration Date of December 2, 2011 as calculated in (c) above is the earlier date in comparison to the 14 Year Cap Date as calculated in (d) above, and since the Extended Term Expiration Date of December 2, 2011 as calculated in (c) above is the earlier date in comparison to the 5 Year Cap Date as calculated in (e) above, the appropriate Patent Term Extension Expiration Date for U.S. Patent No. 5,101,013 is December 2, 2011.

(13) ACKNOWLEGEMENT OF DUTY TO DISCLOSE

Applicant is not aware of any information hereby acknowledges pursuant to 35 U.S.C. § 156(d)(4) and 37 C.F.R. § 1.765 a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought hereunder.

Applicant is not aware of any information and thus, no Information Disclosure Statement is submitted herewith.

(14) PRESCRIBED FEE

The prescribed fee for receiving and acting upon this Application for Patent Term Extension including that required by 37 C.F.R. § 1.20(j) is authorized by the Transmittal Letter which accompanies the instant Application.

(15) CORRESPONDENCE CONTACT

Please direct inquiries and correspondence related to the instant Application to the undersigned at the address below.

(16) DUPLICATE COPIES

Applicant has submitted two copies of this Application in the form of certified duplicates.

(17) DECLARATION

A Declaration of Patent Owner as required by 37 C.F.R. § 1.740(a)(17) and § 1.740(b) has been submitted herewith.

Applicant awaits early notification of a favorable decision granting the requested Patent Term Extension.

Respectfully submitted,

Stephen L. Nesbitt, Reg. No. 28,981
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U.S. Patent No. 5,101,103

Appendices A-H
To Application for
Extension of Patent Term

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APPENDIX INDEX AS SUBMITTED WITH

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

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Appendix C	FDA Approval Letter
Appendix D	Copy of U.S. Patent Number 5,101,013
Appendix E	FDA Acknowledgment Letter
Appendix F	NDA Submission Letter
Appendix G	Summary of Clinical Trials
Appendix H	Chronological Listing of Significant Communications