EXHIBIT E-6

‘933 File History
Paper No. 19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

FU-KUEN LIN

Serial No. 07/113,178 Group Art Unit: 186

Filed: October 23, 1987 Examiner: J. Kushan

PRODUCTION OF ERYTHROPOIETIN

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AMENDMENT UNDER RULE 116

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20036

Sir:

Responsive to the Final Official Action dated September 18, 1989, kindly amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 67-75.

Please add the following new claims:

--76. A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

77. A glycoprotein product according to Claim 76 wherein the exogenous DNA sequence is a cDNA sequence.

78. A glycoprotein product according to Claim 76 wherein the exogenous DNA sequence is a genomic DNA sequence.

79. A glycoprotein product according to claim 76, 77, or 78 wherein the host cell is a mammalian cell.

80. A glycoprotein product according to Claim 79 wherein the non-human eucaryotic host cell is a CHO cell.

81. A pharmaceutical composition comprising an effective amount of a glycoprotein product according to Claim 76 and a pharmaceutically acceptable diluent, adjuvant or carrier.

82. A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a glycoprotein product of Claim 76.

83. A method according to Claim 76 wherein the therapy comprises enhancing hematocrit levels.--

REMARKS

Applicant wishes to express appreciation to Examiners Kushan, Schain and Moskowitz for their time and thoughtful consideration of the issues during the interviews of December 1, 1989 and December 20, 1989, with Mr. Steven Odre. It is believed that the interviews materially advanced prosecution of the subject application.

Reconsideration and allowance of the subject application are respectfully requested.

Claims 67-75 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the invention as set forth in claims 1-11 of commonly owned U.S. Patent No. 4,667,016 ("Lai patent"). Reconsideration is requested.

The Examiner has sought to support the double patenting rejection with the assertion that "the identical source material of the recombinant species of EPO purified by the claimed procedure of the Lai patent will be

indistinguishable from the instantly claimed product" and it was the Examiner's ultimate conclusion that "the recombinantly produced erythropoietin as instantly claimed would have been a prima facie obvious modification of the claimed process of producing recombinant EPO recited in previously patented claims of the Lai patent." The fact that both the starting material and final product of the Lai process (neither of which are claimed in the Lai patent) are included within (dominated by) the recombinant product claims of the present application is not a basis for a double patenting rejection.[1] Applicant respectfully submits that grounds advanced by the Examiner are factually and legally inadequate to support the rejection.

It is well established that all proper double patenting rejections, whether "same invention double patenting " or "obviousness-type double patenting" are based on the fact that a patent has been issued and later issuance of a second patent will continue protection, beyond the date of expiration of the first patent of the very same invention claimed or of a mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art. See In re Kaplan, 229 USPQ 678 (CAFC, 1986). The Examiner has acknowledged that the rejection of the claims in the present invention is not based on "same invention" double patenting. In order for an "obviousness-type double patenting" rejection to be sustained there must be an obvious modification of what is claimed in the first patent, and clear evidence to establish why the modification would have been obvious which can properly qualify as "prior art".

All of the claims of the commonly owned Lai patent relate to a process of purifying erythropoietin including a process of purifying recombinant erythropoietin ("recombinant EPO"). The present

1 The Examiner must not confuse double patenting with "domination" which by itself does not give rise to double patenting. Domination occurs when one patent has claims which "read on" the invention defined by the claims of another patent, thus one patent dominates the other when practicing the invention of the other infringes the dominating patent (see In re Kaplan, supra).

application relates to a recombinant EPO product. The Examiner states that the "recombinantly produced erythropoietin as instantly claimed, would have been a prima facie obvious modification of the claimed process of producing recombinant EPO recited in previously patented claims of Lai et al." Fundamentally, the claims of the Lai patent do not relate to a process of producing recombinant EPO. The claims of the Lai patent relate to a method of purifying recombinant EPO. The recombinant EPO must already be produced before the purification method of Lai et al. can be used. The Examiner states that the recombinant EPO claimed by the present invention is an obvious modification of the Lai purification claims, but does not show what this "modification" to the claims of Lai et al. is, nor can the Examiner, since a method of purifying recombinant EPO cannot be modified to produce recombinant EPO any more than a method of washing a car can be modified to make a car. The Examiner also does not say why the "modification" would have been obvious, and does not cite any prior art to support the contention that the "modification" is obvious.

The Examiner has used the disclosure of the Lai patent as though it were prior art, which it is not, to support the obviousness aspect of the rejection. There is no way the Examiner can find the subject claims to be an obvious variation of what Lai claims except by treating the Lai patent disclosure (which includes a discussion of how to make recombinant EPO by incorporating the parent case of the subject case by reference) as though it were prior art. Use of the disclosure as prior art in a double patenting rejection, has repeatedly been held to be impermissible (see In re Kaplan, supra, In re Vogel, 164 USPQ 619 (CCPA 1970), In re Aldrich, 158 USPQ 311 (CCPA 1968), and In re Boylan, 157 USPQ 370 (CCPA 1968)).

Without a showing or evidence as to what the "obvious modification" of the Lai claimed purification process is and a showing or evidence as to why such a "modification" would be obvious to one of ordinary skill in the art as of the effective date of the Lin application, the rejection of the pending claims under the doctrine of obviousness-type double patenting in view of the Lai patent should be withdrawn.

Should the Examiner maintain the double patenting rejection, the Applicant's Assignee, in view of its immediate need for patent protection, is prepared to file the requested terminal disclaimer if the subject application would then be in condition for immediate allowance and issuance of a patent.

Claims 67-75 also stand rejected under 35 U.S.C. 112 first and second paragraphs. The Applicant has cancelled claims 67-75 without prejudice. These claims will be the subject of a continuation application.

The Applicant has added new claims 76-83, which are similar to cancelled claims 67-75, but which specify that the DNA sequences encode human erythropoietin. These new claims parallel claim 2 of U.S. Patent No. 4,703,008 (Lin '008 patent), the parent of the instant application[2]. The Examiners have indicated during the interview of December 20, 1989, that these new claims would be entered and be allowable.

* * *

During the interview of December 20, 1989, it was indicated that the Examiner would be checking with Examiner-in-Chief Caroff regarding possible suspension of this application pending resolution of Interference Nos. 102,096 (involving the Lin '008 patent) and 102,097 (involving the Lin process application). The Applicant submits that any suspension of prosecution or declaration of an interference would be improper in view of the entire record now before the Patent Office, in particular the new evidence, including the priority determination, in the decision rendered by the United States District Court for the District of Massachusetts in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., and Genetics Institute, Inc., Civil Action No. 87-2617-Y, on December 11, 1989. A copy of that decision is attached hereto. In deciding to declare the above-identified interferences, the Patent Office relied principally upon a Rule 608(b) showing by Fritsch et al. The Court's decision rejected a 102(g) anticipation attack based on Dr. Fritsch's work at Genetics Institute

2 Claim 2 was held valid in the District Court decision referred to herein.

(including the evidence presented in the Rule 608(b) showing by Fritsch et al.), and upheld claims of the Lin '008 patent including the following:

> 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> 4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

In determining that claims 2 and 4 of the Lin '008 patent are valid, the Court recognized that Lin is the first inventor of the DNA sequence encoding human erythropoietin and of the use thereof in a host cell to make recombinant erythropoietin. The discussion on pages 67-84 of the decision evaluates all of the priority evidence which was developed by the parties after extensive discovery and 38 days of trial (including the Rule 608(b) submission by Fritsch et al.). See, for example, the first full paragraph of the decision, pages 67-80, where the Court finds that Lin conceived of the invention before Fritsch et al., as well as pages 80-84 where the Court discusses Fritsch et al.'s lack of diligence.

The decision is thought to be fully dispositive of not only the priority of invention issues in both interferences, and any priority issue in the subject application. Therefore, it is submitted that if Lin was the first to invent the DNA encoding erythropoietin, and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell.

Even if the Examiner believes a priority issue remains in the subject application, the application should still issue as a patent under MPEP 2303. Section 2303 of the MPEP states:

> Interferences will not be declared between pending applications if there is a difference of more than three (3) months in the effective filing dates of the oldest and the next oldest applications, in the case of inventions of a simple character, or a difference of more than six (6) months in the effective filing dates of the applications in other cases, except in exceptional situations, as determined and approved by the group director.

The effective filing date of the subject application as well as Applicant's patent and application involved in the above-noted interferences, is almost thirteen (13) months before the effective filing date of Fritsch et al. (see pages 6-7 of the Amendment filed July 11, 1989 in the subject case).

In declaring Interference 102,097 (involving the process claim) between the Lin application and the Fritsch application, rather than between a Lin patent application and Fritsch application, the Patent Office did not follow the MPEP 2303 six (6) month rule because it relied principally on the Rule 608(b) showing by Fritsch et al. This showing was the only evidence before the Patent Office at the time it was considering declaring the interference.

In the subject application, the Patent Office now has new evidence to consider in determining whether the subject application should be suspended, placed in interference, or permitted to issue. The new evidence is the priority determination in the recent District Court decision. The Court found that the Rule 608(b) showing by Fritsch et al. was insufficient to establish Fritsch et al. as the first inventors of any DNA sequence encoding erythropoietin or the use of such in a host cell to produce recombinant erythropoietin. Therefore, the Patent Office can no longer rely upon the Fritsch et al. 608(b) to establish any basis of priority for Fritsch.

The Applicant submits that in determining whether to immediately issue a patent based on the present application or suspend the present

application pending resolution of the above-identified interferences, the Examiner must consider the irreparable harm that Amgen would suffer by permitting admitted "infringement" of the allowed claims. A suspension of this application pending resolution of interferences which were declared on the basis of a 608(b) showing, now determined to be insufficient after a full hearing in a Federal District Court would be improper and would result in irreparable harm to the Applicant and his Assignee by denying them access to an appropriate forum to seek redress for ongoing infringement activities. Failure to immediately issue the pending claims would allow foreign competition to do what no U.S. company could legally do -- have risk-free access to the U.S. markets. There would be no prejudice to any potential infringing competition by issuance of the claims because all patent defenses would be available and such a party could copy claims of the issued patent and make a proper showing (if possible in view of the Court's holding) and seek to have an interference declared. Therefore, it is respectfully submitted that the present application should not be suspended or placed in an interference and that the application should be permitted to issue promptly.

In view of the above, Applicant respectfully submits that all claims now pending herein fully and patentably define the present invention. Therefore, Applicant requests entry of the Amendment and early receipt of the official Notice of Allowance.

Should any matters remain outstanding, the Examiner is encouraged to telephone Applicant's undersigned attorney collect at (805) 499-5725, so that same can be resolved without the necessity of an additional action and response thereto.

Respectfully submitted,

January 10, 1990

By _____

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