EXHIBIT 37

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

FRITSCH ET AL.	)	
	)	
v.	)	Interference No. 102,334
	)	
LIN	)	Examiner-in-Chief:
	)	Marc L. Caroff

BOX INTERFERENCE

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DECLARATION OF THOMAS W. STRICKLAND

Hon. Commissioner of Patents
and Trademarks
Washington, D. C. 20231

Sir:

I, THOMAS W. STRICKLAND, do solemnly declare as follows:

1. I am the same Thomas Wayne Strickland who executed a declaration November 30, 1988, (hereinafter the "Strickland Declaration") in connection with the U.S. patent application of Fu-Kuen Lin, Serial No. 113,178, filed October 23, 1987 (hereinafter the "Lin application").

2. Since the execution of the Strickland Declaration, I continue to be employed by Amgen Inc., Thousand Oaks, California, and currently hold the position of Research Scientist III.

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3. In addition to the experience noted in paragraph 2 of the Strickland Declaration, I would note that I received my Ph.D. from Vanderbilt University in 1981, where the subject of my thesis was glycoprotein hormones. I thereafter have spent my entire professional career in the field of glycoproteins and erythropoietin. A copy of my curriculum vitae is attached as Exhibit A hereto.

4. In addition to the Lin application noted above, I have read the Declaration of Dr. Dale A. Cumming dated March 14, 1990, submitted in Interference No. 102,334 (the "Cumming Declaration") as well as the attachments thereto. Also, I have read Motions I, II, III and IV of the 37 CFR §§1.633 and 1.635 Motions by Fritsch et al. and the attachments thereto filed in Interference No. 102,334. Further, I have read the specification of the Lin application and U.S. patent application No. 675,298 filed November 30, 1984 in the name of Fu-Kuen Lin (the "Lin IV application") as well as the following US patent applications:

S.N. 561,024, filed Dec. 13, 1983 (the "Lin I application");
S.N. 582,185, filed Feb. 21, 1984 (the "Lin II application"); and
S.N. 655,841, filed Sept. 28, 1984 (the "Lin III application").

5. I note that the Lin application involved herein and the Lin IV application are identical in text.

6. There is nothing in any of the documents referred to in paragraph 4 above that changes my opinion that recombinant erythropoietin ("rEPO") as described and claimed by the Lin application has a different carbohydrate composition than that of the naturally occurring urinary erythropoietin ("uEPO").

7. Referring to paragraph 4 of the Cumming Declaration, I would note that although the term "carbohydrate composition" is used to refer to the content of individual monosaccharrides, the carbohydrate composition of a glycoprotein also includes the structure, linkages, and relative proportions of oligosaccharrides. Even accepting the narrower definition of Dr. Cumming, the Strickland Declaration unambiguously demonstrates that rEPO produced according to Example 10 of the Lin application and uEPO differ in their monosaccharide composition, as discussed more fully in paragraphs 8, 9 and 10 below.

8. In paragraph 5 of his declaration, Dr. Cumming apparently disregarded the procedures outlined in SD-8[1]. Dr. Cumming incorrectly states in paragraph 5 of his declaration:

[1] For ease of reference, portions of the Strickland Declaration will be referred to as "SD-" followed by the relevant paragraph number. Likewise, the Cumming Declaration with be referred to by "CD-" and relevant paragraph.

> "The experiments compared sialidase and endoglycosidase treated uEPO and rEPO isoforms and simply showed the enzymatically treated uEPO carried a greater charge." (emphasis supplied)

The error of this statement is borne out by paragraph 8 of the Strickland Declaration which states:

> 8. Separate aliquots of r-HuEPO and u-EPO, each containing approximately 5 μg of the respective protein, were subjected to isoelectric focusing in a polyacrylamide gel in the presence of 5M urea essentially in accordance with the procedure described by LKB Technical Bulletin #2217 (Exhibit "D").

Thus, SD-8 relates to untreated aliquots of rEPO and uEPO (i.e., no enzyme treatment). This conclusively demonstrates that a difference exists in the charge of the rEPO and uEPO materials. The subsequent enzymatic analysis reported in SD-9 was carried out to determine whether the more acidic nature of uEPO reported in SD-8 was due to differences in the protein or carbohydrate composition of the EPO molecule. In order to determine the causative factor for the more acidic nature of the uEPO, it was necessary to compare the relative charges of the uEPO and rEPO polypeptide by enzymatically digesting the respective molecules to remove the carbohydrates therefrom (see SD-9 at page 9). Thus, the experiments compared untreated rEPO and uEPO isoforms as well as enzymatically treated rEPO and uEPO. The data in SD-9 clearly supports the conclusion of SD-11 that the more acidic nature of uEPO is due to a difference in carbohydrate composition.

9. The use of isoelectric focusing in SD-8 & 9 compared results of both untreated and enzymatically treated urinary and recombinant EPO in order to determine differences in carbohydrate composition. Dr. Cumming overlooks or disregards SD-8 relating to the untreated EPO. Indeed, isoelectric focusing is a conventional and well accepted means to evaluate variable carbohydrate composition as is evidenced in a product brochure of the LKB Corporation entitled, "Isoelectric focusing of monoclonal antibodies in immobilized pH gradients," attached hereto as Exhibit B[2]. As quoted from this brochure the cause of multiple components of monoclonal antibodies when subjected to isoelectric focusing, "[t]he microheterogeneity is thought to be due to a differential loss of labile amido groups and to a variable carbohydrate composition." (emphasis added)

10. Since the carbohydrate moieties of uEPO are more negative than rEPO, the uEPO carbohydrate moieties must contain a greater number of negatively charged monosaccharide units than are present in rEPO. As stated in SD-10, the nature of these excess negative charges is not fully known. However, it is irrefutable that the greater negative charge of the oligosaccharides of uEPO when compared to rEPO must result from either quantitative (such as a greater number of sialic acid residues) or qualitative (such as the presence of sulfated monosaccharides) differences in the monosaccharide

[2] It is art recognized that monoclonal antibodies are glycoproteins.

content of the two preparations. Thus, even accepting the limited definition of average carbohydrate composition given by Dr. Cumming (CD-4), these results demonstrate that the carbohydrate composition of rEPO differs from that of uEPO.

11. I note that at no point does Dr. Cumming state that the carbohydrate compositions of rEPO and uEPO are the same, and indeed such a statement cannot validly be made with support. The simple fact of the matter is that the carbohydrate composition of rEPO differs from that of uEPO. This difference is further supported by Takeuchi et al., J. Biol. Chem., Volume 263, No. 8, pp. 3657-3663 March 15, 1988 (Exhibit C attached) which states on page 3659:

> ...The total amount of complex-type oligosaccharides with N-acetyllacetosamine repeating units in their outer chain moieties accounted for 34.5% in the case of rHuEPO, which was approximately five times higher than that of urinary HuEPO (7.5%). All sialic acid residues in the sugar chains of rHuEPO occur as the NeuAcα2-3Gal group, while about 60% of those of urinary HuEPO occur as the NeuAcα2-3Gal group and the others occur as the NeuAcα2-6Gal linkages."

The same authors also find an excess of sialidase resistant negative charges of uEPO as opposed to rEPO (See Fraction A-7 of Figure 1, page 3658). The authors suggest at page 3658 that these negative charges may indicate the presence of excess sulfate groups in the oligosaccharides of uEPO. Once again, this difference in negative

charge can only be attributed to a difference in the individual monosaccharide components of the two materials.

12. The statements of Egrie et al. and Browne et al. referred to by Dr. Cumming do not support the inferences drawn. The statements are taken out of context both as to time and substance. As noted in paragraph 5 above, the data which appear at page 65 of the Lin application are identical to the data in the Lin IV application filed in 1984. The Egrie et al. and Browne et al. articles appeared in 1986. Amgen's Product License Application was filed in October, 1987. The isoelectric focusing data was obtained in July, 1988, and was submitted to the FDA in writing in August, 1988 (see Exhibit E hereto and ¶15 below). These data form the basis of the Strickland Declaration dated November 30, 1988 which was submitted to the Patent Office. Nowhere in these documents is the statement made that the carbohydrate composition of rEPO is the "same" as that of uEPO, and in fact, such a statement cannot be made. Furthermore, the statements contained in the Egrie et al. and Browne et al. papers are not inconsistent with the statement at page 65, lines 27-29 of the Lin application as well as the representations made to the FDA in Amgen's PLA.

13. Dr. Cumming states (CD-9) that based on his experience and the literature relating to the carbohydrate composition of uEPO and rEPO, "the hexose composition of urinary erythropoietin and recombinant erythropoietin cannot be distinguished from each

other." This statement by Dr. Cumming is directly in conflict with published literature as evidenced by a comparison of the hexose values (mannose + galactose) provided by Dordal et al. Endocrinology, Vol. 118, No. 6, 2293-2299 (1985) (Exhibit D attached) which compare as follows with the average hexose value (± standard deviation) from the 6 lots of rEPO set forth in Figure 9.C-1 of Amgen's Product License Application.

	rEPO (Amgen's PLA)	uEPO (Dordal α)	uEPO (Dordal β)
Hexoses[1]	1.52±.08	1.67	2.11

[1] Normalized to the N-acetyl glucosamine content.

Thus, these values illustrate a difference in values for the hexose composition of Amgen's rEPO from that of uEPO reported by Dordal et al.

14. The submission of data in Amgen's PLA is consistent with the statement contained in SD-11. For example, pages 0765, 0791, 0796, 0799, 0898, 0905 and 0906 clearly evidence differences which exist in the carbohydrate composition between Lin's recombinant EPO and urinary EPO. Neither the data reported in the Strickland Declaration nor that presented in Amgen's PLA asserts that the average carbohydrate compositions "are the same". The data presented in Figure 9.C-9 of Amgen's Product License Application ("PLA") (Page 0905) directed to the structures and relative proportions of the N-linked oligosaccharides of rEPO and uEPO illustrates a number of differences in the carbohydrate composition of the two materials. For example, the

relative population of each oligosaccharide is different between rEPO and uEPO (See page 0906-right four columns). The presence of excess sialidase resistant negative charges on the carbohydrate of uEPO was also described on page 0796 of Amgen's PLA.

15. In the Fritsch Motions I and II, I note that alleged material fact 5 suggests evidence was omitted from the Strickland Declaration. No material evidence was omitted from my declaration. As noted in ¶12 above, the data contained in the Strickland Declaration was obtained subsequent to submission of Amgen's PLA and in fact was provided to the FDA as evidenced by Exhibit E attached hereto. I know of no evidence that is inconsistent with the Strickland Declaration

16. In Fritsch Motion IV it is stated that the Lin I, II and III applications "are silent on any enablement with respect to a difference in average carbohydrate composition." Based on my personal experiences in the analyses of rEPO and uEPO as well as the literature relating to the carbohydrate compositions of glycoproteins including uEPO and rEPO, each of the Lin I, II, and III applications provide sufficient information to one skilled in the art to prepare rEPO from expression in a non-human eucaryotic host cell having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

With reference to the Lin I application I would note that the application clearly describes the use of yeast cells and mammalian cells at page 47. These are examples of non-human eucaryotic host systems. In like manner, I find the same teaching as presented in the Lin I application to be provided in the Lin II application at pages 54-55.

Further, I note that Example 10 of the Lin III application corresponds to Example 10 of the Lin IV application, and hence, to Example 10 of the Lin application. Example 10 of the Lin III application produces a recombinant EPO product having an average carbohydrate composition which differs from that of naturally occurring human EPO for the reasons given in the Strickland Declaration.

17. Based on the disclosure of the Lin application, my work as reported in the Strickland Declaration, the exhibits hereto, my professional experience in the field of carbohydrate biochemistry, particularly as related to rEPO and uEPO, it is still my firm opinion that the average carbohydrate composition of rEPO as described and claimed in the Lin application differs from the average carbohydrate composition of uEPO.

I further declare that 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 Section

1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Thomas W. Strickland

Thomas W. Strickland

Date 4/5/90