EXHIBIT 36

IN THE

UNITED STATES PATENT and TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

Interference No. 102,096
Interference No. 102,097
and
Interference No. 102,334

FRITSCH

v.

LIN

Examiner-in-Chief Marc L. Caroff

PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW FOR THE PARTY FRITSCH

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Abbreviations Used In Citations

FROM FRITSCH'S RECORD:

FR ___	**Testimony on Fritch Record pages**
FX ___	**Fritsch Exhibit**
FCX ___	**Fritsch Cross Exhibit**

FROM LIN'S RECORD

LR ___	**Testimony on Lin Record pages**
ITC Hearing ___	**Testimony from ITC hearing submitted by Lin under Rule 682(a)**
Tr. Vol. _____	**Testimony from district court action in Boston submitted by Lin under Rule 682(a)**
LX ___	**Lin Exhibits**
PX ___	**Trial Exhibits from district court action in Boston submitted by Lin under Rule 682(a)**
A _____	**Pages from Parties Joint Appendix (submitted to Federal Circuit on appeal of district court decision) submitted by Lin under Rule 682(a)**

VI. LIN'S '178 APPLICATION DOES NOT DESCRIBE OR ENABLE THE PRODUCTION OF RECOMBINANT HUMAN EPO HAVING A CARBOHYDRATE COMPOSITION WHICH DIFFERS FROM THAT OF NATURAL HUMAN EPO AND LIN'S CLAIMS ARE UNPATENTABLE UNDER § 102(b)

A. PROPOSED FINDINGS OF FACT

General Finding No. 5.1

The carbohydrate composition of the recombinant human EPO product described in Lin's '178 patent application does not differ from the carbohydrate composition of the natural EPO product described by Miyake et al. in 1977; the '178 application claims are anticipated by Miyake et al.

VI-1. Count 1 purports to claim a novel EPO-like glycoprotein defined as (1) a non-naturally occurring glycoprotein, (2) being the product of the expression in a non-human eucaryotic host cell of the DNA sequence encoding EPO, (3) possessing in vivo biological activity and (4) having an "average carbohydrate composition which differs from that of naturally occurring human erythropoietin."

VI-2. Count 1 is identical to claim 76 of the involved '178 Lin application, and each of claims 76-83 corresponding to the count contains the limitation that the EPO glycoprotein have "an average carbohydrate composition which differs from that of naturally occurring human erythropoietin."

VI-3. The term "average carbohydrate composition" is conventionally used and understood by scientists skilled in the art of glycoproteins to define the proportions of the monosaccharide components present in a glycoprotein. The term is used in this sense in Example 10 of the involved Lin '178 application at p. 65,

lines 10-21, wherein the results of analyses of individual carbohydrate components present in urinary EPO (uEPO) and recombinant EPO (rEPO) are given. LR '334, 98 (Strickland); FR 5258 (Cumming). "Carbohydrate composition" is also used in the Amgen Product License Application ("PLA") to the FDA to connote the proportions of individual monosaccharide components present in Amgen's rEPO. FR 5260-61 (Cumming); LR '334, 724-725 (Strickland); FX 399 (at p. 792, 889-890).

VI-4. The only data for carbohydrate composition set forth in the involved Lin '178 application is found at page 65, lines 10-21. This data indicates the monosaccharide content expressed as normalized molar ratios for uEPO and rEPO, but fails to establish that Lin's rEPO has an "average carbohydrate composition" different from naturally occurring (urinary) EPO. Table A below summarizes that carbohydrate composition data.

Table A

Monosaccharide Component	u-EPO	r-EPO
Hexoses	1.73	15.09
N-Acetylglucosamine	1	1
N-Acetylneuraminic	0.93	0.998
Fucose	0	0
N-Acetylglucosamine	0	0

VI-5. The data in the Lin application shows that all monosaccharide components in uEPO and Lin's rEPO are comparable

except for hexoses. Although the numerical data for the sialic acid component is not precisely identical for uEPO and rEPO, the values (0.93 and 0.998) are indistinguishable within the limits of analytical error. FR 5259 (Cumming). In fact, there is no difference in the sialic acid content of rEPO and uEPO. The Sasaki et al. (1987) paper, FX 626, indicates that uEPO contains a sialic acid content of 10.4 moles/mole, which is encompassed by and indistinguishable from the range of 9.5 to 11.8 moles/mole for rEPO. FR 4083-84 (Cumming). Accordingly, the molar ratio value of 15.09 for hexoses in Lin's rEPO is the only basis for the limitation that the rEPO product differs in average carbohydrate composition from naturally occurring EPO.

VI-6. The hexose value of 15.09 exceeds the average value reported in the literature for hexose saccharide components by a factor of nearly 10 and is erroneous. FR 5259-60 (Cumming).

VI-7. The hexose carbohydrate composition data in the Lin application has been shown to be invalid and unreliable for other reasons. This data is derived from a certain carbohydrate analysis performed by Dr. Yu in late 1984 on two rEPO samples, B and C, and one uEPO sample, A. [See LX 81, Doc. Nos. L00867-869]. Example 10 of the Lin application incorporates the Yu data for sample A and sample C; LR 276-277, 279-280, 312 (Lin). However, Dr. Yu's data indicates that the total mass of the various carbohydrate components alone exceeded the mass of the rEPO sample itself. This is a clear impossibility, LR '334, 861-862 (Yu); LR 308-310 (Lin); LX 81 (Doc. No. L00868), and the reported

contribution of one or more carbohydrate components is incorrect by a substantial margin. Because such component contributions were used to calculate the molar ratios of the various types of carbohydrate moieties, at least one of the molar ratio values determined by Dr. Yu is far in excess of the true value. FR 5301-02 (Cumming).

VI-8. Dr. Yu apparently looked for fucose and N-acetylgalactosamine in the uEPO and rEPO samples [LX 81, doc. no. L00873], but he reported no results. Similarly, the Lin application reports a value of zero for N-acetylgalactosamine. More recent analyses on different rEPO samples confirm the presence of both of these monosaccharides. See, e.g., Sasaki et al., J. Biol. Chem. 262:12059-12076 (1987). FX 626. A correct analysis should have revealed the presence of those monosaccharides. FR 5303, 3935-36 (Cumming).

VI-9. Another reason why the Yu carbohydrate data in the Lin application is invalid is that it records mannose : galactose ratios for rEPO samples B and C of 59.1 : 1 and 13.15 : 1, respectively, in contrast with the ratio of 0.1 : 1.0 for uEPO Sample A. See LX 81 (doc. nos. L00869, L00868, L00874); LR 306-308 (Lin). The mannose : galactose ratios for these rEPO samples are unusual and cannot be rationalized with what is known of the glycosylation of mammalian proteins. For example, Sasaki et al., (FX 626), have shown by carbohydrate compositional analysis that uEPO and CHO rEPO yield mannose : galactose ratios 0.5 to 0.1 : 1. These discrepancies between the Yu analysis and later published

results are a strong indication that the molar ratios for hexose disclosed by Lin are incorrect. FR 5304, 3937, 3940-42 (Cumming).

VI-10. Lin's rEPO sample B had "too much mannose contamination," and rEPO sample C was "better." LX 81 (doc. nos. L00867 and L00869). There is no indication that the sample contamination problem had been resolved, and contamination is consistent with the exaggerated hexose molar ratios reported in the Lin application for sample C. FR 5304 (Cumming).

VI-11. Amgen's Dr. Strickland has acknowledged that the normalized molar ratio value for hexose as reported in the Lin application is not representative of rEPO and, in constrast to the 15.09 value in the Lin application, he has never seen a carbohydrate analysis indicating a normalized hexose content which exceeded 2.0. LR '334, 732-734 (Strickland).

VI-12. That the hexose values for rEPO reported in the Lin application are erroneous is also shown by data in the literature and in Amgen's own Product License Application ("PLA") to the FDA. FX 399.

VI-13. A comparison of various data on the carbohydrate compositions of human uEPO and rEPO, as reported in the literature, establishes that there is no statistical difference between the average carbohydrate composition of human uEPO and rEPO. FR 5269 (Cumming). Both contain the same monosaccharides in the same general proportions. FR 5269 (Cumming). An examination of all available data in the published literature, Takeuchi et al. (1987), FX 625, Sasaki et al. (1987), FX 626, Dordal et al. (1985),

FX 629, and the Amgen PLA, FX 399 at p. 890, reveals that the average carbohydrate compositions of rHuEPO and uHuEPO cannot be distinguished from each other. FR 5269-5274 (Cumming).

VI-14. Further evidence of identity is found in the Amgen PLA, (FX 399 at p. 792, 889-890) which sets forth the average carbohydrate composition of 6 lots of rHuEPO expressed by mammalian CHO cells transfected with the EPO gene. The average hexose content for each of the six lots ranges from 1.44 to 1.66. This hexose content of rEPO cannot be distinguished from the average of values reported in the literature for the hexose content of uEPO. Thus Amgen's PLA reports a hexose value of 1.66 for one lot of rEPO, which is no different from the hexose value of 1.67 reported by Dordal et al. (FX 629) for natural EPO. FR 5260-61, 5270-5273 (Cumming).

VI-15. The average hexose value for Amgen's human rEPO is alleged by Lin to be 1.52 +/-0.08. This value is not distinguishable from the average value of 1.57 for the hexose content of human uEPO as published in the literature. Similarly, comparing all published data for human uEPO with the data in Amgen's PLA and Takeuchi et al. (1987) (FX 625) for Amgen's human rEPO, the average normalized value for hexose in human rEPO is 1.47 +/-0.13, which is indistinguishable from the average normalized hexose value of 1.49 +/-0.41 in human uEPO. FR 5271-72 (Cumming).

VI-16. By further averaging the hexose values for human rEPO, as reported in Sasaki et al., (FX 626) with the values

reported in the Amgen PLA (FX 399 at p. 890) and by Takeuchi et al. (1987), (FX 625), the resultant average normalized hexose value of 1.39 +/-0.16 is obtained. This is indistinguishable from the average normalized hexose value of 1.36 reported by Sasaki et al. (FX 626) for human uEPO. FR 5273 (Cumming).

VI-17. Example 10 of the Lin application, page 64, line 20 to page 65, line 3, reports a western blot analysis of SDS-PAGE gels of untreated and enzymatically treated CHO cell-produced rEPO and a partially purified pooled uEPO sample provided by Dr. Eugene Goldwasser. The analysis is stated to reveal a difference in apparent molecular weight. However, no information relevant to a difference in the average carbohydrate composition can be obtained from such western blot, SDS-PAGE analyses. FR 3951-53 (Cumming). Morever, an entry in Dr. Egrie's own notebook No. 633 dated 9/19-9/21/84 states that Amgen's rEPO appeared to be the same size as a uEPO sample obtained from Alpha Therapeutics and a uEPO sample designated as "Lot 82." LX 115, (doc. no. L01074). Dr. Egrie has acknowledged that the uEPO and rEPO samples migrated identically on the SDS-polyaccrylamide gel. LR 577-579 (Egrie). Because all known uEPO samples are prepared from pooled sources, as was the uEPO referenced in Example 10, the unequal-weight observations described in Example 10 of the Lin application are clearly contradicted by the Egrie notebook data. FR 5305, 3955, 4078-79 (Cumming).

VI-18. Further, an article co-authored by Dr. Egrie and other scientists at Amgen reports that "the carbohydrate

composition of purified rHuEPO...is very similar to that determined for natural EPO..., indicating both the carbohydrate composition and number of carbohydrate chains of the EPO produced by the two different cell types (human kidney and Chinese hamster ovary) are very similar." Egrie et al., "Characterization and Biological Effects of Recombinant Human Erythropoietin, Immunobiol. 172:213-224 at 223 (1986). FX 395 at p. 223. This is consistent with the statement, published by Amgen's scientists in Brown et al., "Erythropoietin: Gene Cloning, Protein Structure, and Biological Properties," Cold Spring Harbor Symposia on Quantitative Biology" 51:693-702 at 698 (1986), that "[h]uman urinary EPO and CHO-cell-derived r-hEPO migrate identically in SDS-polyacrylamide gels, indicating that both molecules are glycosylated to a similar extent... The carbohydrate composition of r-hEPO was essentially the same as that of urinary EPO..." FX 396 at p. 698.

VI-19. The facts and admissions set forth in Amgen's PLA also prove that there is no significant difference in the carbohydrate moieties of uEPO and the rEPO produced commercially by Amgen. Amgen's PLA document (FX 399) confirms "the similarity of the secondary and tertiary protein structures of r-HuEPO and u-HuEPO as predicted by the equivalence of their immunological and biological activities ... ." FX 399 at p. 782 "All physical tests performed on both r-HuEPO and u-HuEPO ... show these proteins to be indistinguishable ..... The amino acid sequences ... are identical. The two disulfide bonds and four glycosylation sites found in r-HuEPO are identical to those found in u-HuEPO .... The

molecular weight of r-HuEPO agrees well with figures reported in the literature for u-HuEPO." FX 399 at p. 789.

VI-20. "Both r-HuEPO and u-HuEPO contain three asparagine-linked (N-linked) and one serine-linked (O-linked) carbohydrate groups. As is commonly observed with glycoproteins, the carbohydrate moieties of r-HuEPO and u-HuEPO exhibit microheterogeneity, resulting in populations containing oligosaccharides of different but related structures. The sequence data indicates that, although the relative proportions differ somewhat between r-HuEPO and u-HuEPO, they both contain the same set of oligosaccharide structures." FX 399 at p. 791.

VI-21. "Endoglycosidase F (Endo F), an enzyme which removes N-linked oligosaccharides, reduces the apparent molecular weight of both r-HuEPO and u-HuEPO from about 36 Kd to about 21 Kd. Both erythropoietin preparations also display a minor band at about 18 Kd after Endo-F digestion. Further digestion of Endo-F treated erythropoietin with sialidase and O-glycanase ..., which removes the Gal-GalNAc core of O-linked oligosaccharides, reduces the molecular weight of the 21 Kd fraction of both preparations to about 18 Kd. ... These enzyme digestion experiments confirm the presence of an O-linked oligosaccharide in both r-HuEPO and u-HuEPO. The small amount of material migrating at 18 Kd after only Endo-F digestion suggests that a minor population of r-HuEPO and u-HuEPO lacks this O-linked oligosaccharide." FX 399 at 793.

VI-22. "Tetra-antennary oligosaccharides are most prevalent on both r-HuEPO and u-HuEPO. Both preparations contain

lesser amounts of tri-antennary and bi-antennary structures. ... [A]ll of the oligosaccharide structures present on r-HuEPO are also found on u-HuEPO .... [T]he sialic acids of both r-HuEPO and u-HuEPO consist solely of N-acetylneuraminic acid." FX 399 at 799.

VI-23. "In summary, it is concluded that the differences between r-HuEPO and u-HuEPO oligosaccharide populations are not significant. Furthermore, the most relevant findings ... are the overall similarity of the oligosaccharide structures and the demonstration that all of the carbohydrate structures in r-HuEPO are also found in u-HuEPO." FX 399 at 800.

General Finding 5.2

As a matter of law, the November 30, 1988 Strickland declaration is ineffective to establish that rEPO has a carbohydrate composition which differs from that of naturally occurring EPO.

VI-24. In the first office action in the involved '178 Lin application, paper no. 4, the examiner rejected the original application claims directed to the "average carbohydrate composition" limitation under 35 U.S.C. §112 for lack of enablement and for failing to particularly point out and distinctly claim the invention. Paper No. 4 at pp. 3-4. Further, the examiner rejected claims 40-41 (the predecessor claims to those corresponding to the count) as anticipated by or obvious over Miyake et al. under 35 U.S.C. §§ 102(b) and 103. The examiner pointed out that Miyake et al. disclosed "two forms of glycosylated EPO" as well as "asialo-EPO" and that "variants of human EPO with the amino acid sequence,

biological activity and difference in degree of carbohydrate composition as claimed by applicant are shown by Miyake et al." Id. at pp. 8-9.

VI-25. In response to the rejection of the claims, Lin submitted an amendment dated December 1, 1988 (paper no. 6) accompanied by the Rule 132 declaration of Dr. Strickland, dated November 30, 1988 (paper no. 7). LR '334 133-149EE. The Strickland declaration was alleged to present results which evidenced "differences in the carbohydrate structures of products of the present invention and urinary-derived erythropoietin," and that urinary and recombinant erythropoietin are "clearly distinct from each other in terms of glycosylation." Paper No. 6 at pp. 9-10. Specifically, Lin argued that the "urinary isoforms consistently displayed lower (more acidic) isoelectric points than the recombinant product isoforms, and that the results of enzymatic digestion of the recombinant and urinary products "revealed that the differences in isoelectric points ... were not attributable to amino acid composition but rather to differences in carbohydrate composition." Id. at pp. 11-12.

VI-26. In the amendment, Lin represented that "the work described in the Strickland declaration ... stands as testimony to the differences between Applicant's products and those of Miyake et al. In sum, Applicant's products are indeed novel." Id. at p. 12.

VI-27. Based upon the applicant's representations and the Strickland declaration, the examiner withdrew the rejection

based on § 102, stating that "applicant has shown through the declaration of Strickland and via the disclosure of Takeuchi et al. that there is a difference in the overall carbohydrate composition between the naturally occurring and recombinant species." Paper No. 8 at pp. 4-5. Thus, the Strickland declaration was submitted to demonstrate the claimed difference in the "average carbohydrate composition" of recombinant erythropoietin and urinary erythropoietin and was accepted by the examiner as such.

VI-28. The 11/30/88 Strickland declaration did not present any new data concerning the relative proportions of the monosaccharide components of rEPO and uEPO. Instead, it reported isoelectric focusing gel experiments which compared isoforms of uEPO and rEPO treated with sialidase and N-glycanase. From those experiments Dr. Strickland concluded that the uEPO isoforms were more negative (acidic) than the rEPO isoforms, and that the more acidic nature of the uEPO isoforms were associated with the sialic acid residues of carbohydrates. Specifically, Dr. Strickland concluded that "the more acidic nature of the u-EPO isoforms compared to the r-HuEPO isoforms, is due to the differences in carbohydrate composition, in particular carbohydrate structure, of r-HuEPO and u-EPO." From this, Dr. Strickland inferred that uEPO and rEPO have "a different carbohydrate composition than naturally occurring urinary erythropoietin." LR '334, 147 (Strickland).

VI-29. For several reasons, however, the evidence in the 11/30/88 Strickland declaration does not establish any difference in the average carbohydrate composition of uEPO and the

rEPO of Example 10 of the '178 application. FR 5258-59 (Cumming). Most importantly, one cannot determine quantitative differences in the average carbohydrate composition between rEPO and uEPO from an isoelectric focusing gel. Indeed, the technique is useless for that purpose. FR 5275-76, 4044-47 (Cumming).

VI-30. Even if the isoelectric focusing technique could reveal differences in the average carbohydrate composition of uEPO and rEPO, the Strickland evidence does not establish that Lin's rEPO described in Example 10 is any different than the uEPO of the prior art. First, the 1988 rEPO and uEPO sample analyzed by Dr. Strickland cannot be accepted as representative of the rEPO uEPO materials prepared and analyzed in 1984 and described in the '178 Lin application. The carbohydrate composition of a recombinant EPO product can be affected by the particular host cells used for expression, LR. 1008, 1009 (Browne), FR 5306, 3972-73, 4087 (Cumming), and/or the purification procedure used LR 249, 251, 252 (Lin); LR '334, 721-723 (Strickland); FR 5306, 4086-89, 4101-02 (Cumming).

VI-31. Lin has provided no information that the cells used to produce the samples analyzed in 1988 were identical to those employed in 1984. In fact, they were not the same. The 1984 rEPO was produced from a heterogeneous pool of cells, whereas the 1988 rEPO material was derived from a single cell line in the Amgen master working cell bank. FR 5306,3966-67 (Cumming); LR '334 629-632 (Strickland); LR 982, 985-986, 1002-1003 (Browne); FCX 2.

VI-32. Further, the purification procedure used for the 1988 rEPO and uEPO samples was clearly different from those used for the 1984 samples. LR '334, 629-631, 679-680 (Strickland); LR 265-267, 269-270, 274-276 (Lin); 11/30/88 Strickland Declaration; LR '334, 133-149EE at 134; LX 81 (doc. nos. L00869, L00864, L00865, L00866, L00867); FR 5306 (Cumming). The identification of different isoforms can be traceable to the use of non-identical purification procedures in the preparation of the rEPO and uEPO samples. FR 5308 (Cumming). Thus, there is no substantiation that the 1988 experimental data is valid for the rEPO produced in 1984 and disclosed in the Lin application. FR 5306 (Cumming).

VI-33. Second, even if the 1988 rEPO and uEPO samples analyzed by Dr. Strickland were representative of the 1984 rEPO and uEPO samples, the Strickland experiments fail to show the existence of a recombinant EPO product "having an average carbohydrate composition which differs from that of naturally occurring human EPO." FR 5307 (Cumming).

VI-34. Dr. Strickland's conclusion of a difference in carbohydrate composition is founded on the alleged observation in a Coomassie-blue stained gel that untreated uEPO is more negative in charge than rEPO, and that the uEPO treated to remove N-linked carbohydrates and all remaining sialic acid residues should reveal identical IEF banding to the similarly treated rEPO. From such an observation Dr. Strickland drew a conclusion that the initial, more negative isoforms of uEPO are attributable to sialic acid residue

differences. LR '334, 100-101, 137-143, 675-676, 689 (Strickland). However, in order to support that conclusion, the isoelectric points of untreated uEPO (lane 4) must be more acidic (negative) than the untreated rEPO (lane 1), and the N-glycanase/sialidase treated rEPO (lane 3) and uEPO (lane 6) must be identical. In fact, they were not identical. FR 5309 (Cumming).

VI-35. Unknown to the PTO, the isolectric focusing gel of the Strickland declaration also had been stained with silver stain which was not submitted to the PTO. LR '334, 667-669 (Strickland). This silver-stained gel (FCX 10/FX 617) reveals additional bands in the treated uEPO lanes (5 and 6) that were essentially invisible in the photograph of the same gel when stained with Coomassie Blue. LR '334, 669-674 (Strickland). If Dr. Strickland had properly considered the additional bands visible in the silver-stained isoelectric focusing gel, he could not have reached the above conclusion. FR 5309 (Cumming).

VI-36. The silver-stained gel (FCX 10/FX 617) shows common banding in the untreated samples (boxed in green in lane 4), which is not disclosed in the declaration and which indicates that both rEPO and uEPO have common isoforms. The gel also shows extra acidic bands in the untreated uEPO (lane 4), which are visible above the isoforms boxed in green. Extra acidic bands are also visible in the N-glycanase treated uEPO (lane 5) and in N-glycanase/sialidase treated uEPO (lane 6), also boxed in green. LR '334, 669-674 (Strickland). These acidic bands present in enzymatically treated uEPO are either absent from or less prevalent

in rEPO (lane 3) and most likely contribute to the additional more acidic bands in the untreated uEPO (lane 4). FR 5309-10 (Cumming). FCX 10; FX 617.

VI-37. Dr. Strickland did not take into account extra bands in lanes 5 and 6 which are potential extra isoforms. LR 673, 687-688 (Strickland). Dr. Strickland's conclusion is crucially dependent on the isoforms in lanes 3 and 6 being identical; but they are not identical. FR 4105-07, 5309 (Cumming). Because the N-glycanase/sialidase treated uEPO and rEPO did not result in identical isoelectric bands, it cannot be concluded that the extra acidic bands in the uEPO sample represent glycosylation differences. Such additional acidic forms are consistent with incomplete sialidase digestion of the EPO, as well as with deamidated or other modified polypeptide isoforms, i.e., acidic forms which are not attributable to glycosylation differences. FR 5310, 3978, 3989-90, 4011-4014, 4089-90 (Cumming). Dr. Strickland utilized no controls to exclude such factors as causes for the more acidic isoforms observed for uEPO even though tests were available to do this. FR 3990-91, 4081-82 (Cumming).

VI-38. Relying on an experiment described in paragraph 10 and reflected in the gel on page 14 of the 1988 declaration, LR '334 at 144-147, Dr. Strickland hypothesized that the more negative isoforms of untreated uEPO results from either a greater number of sialic acid residues or sulfated monosaccharide differences. LR '334 at 147. This hypothesis is flawed for a number of reasons. First, rEPO (Amgen GMP lot 516) and twelve-year old ß-EPO (prepared

in 1976 by the method of Miyake et al.), FX 515; LR '334, 134-136, 144 (Strickland), were treated with sialidase and analyzed on an isoelectric focusing gel. This ß-EPO is not the same uEPO sample that was used in the isoelectric focusing experiments described in paragraphs 8 and 9 of the 1988 declaration. LR '334 at 134-136 (Strickland). No test of the equivalence of the samples was presented, and the ß-EPO cannot be taken as representative of the other uEPO. FR 4041-43 (Cumming). Therefore, any conclusions that may have been drawn from an analysis of the ß-EPO sample described in paragraph 10 cannot properly be attributed to the uEPO sample in paragraphs 8 and 9 and vice versa. FR 5311-12 (Cumming).

VI-39. Second, because of its age (12 years), the uEPO sample could have been deamidated to a significant degree, FR 4038 (Cumming) which would cause it to exhibit acidic isoforms not attributable to carbohydrate differences. Dr. Strickland acknowledges that deamidation can cause isoforms to appear more negative (acidic) than they would without deamidation. LR '334, 700-702 (Strickland); FR 5312 (Cumming). Isoelectric focusing gels are a conventional and well accepted means to evaluate deamidation or other charge modifications of polypeptides. FR 5312-5313 (Cumming). Indeed, the ß-EPO used in that gel has been reported to have fewer sialic acid residues yet appear more negative in SDS gels than another purified fraction. Dordal et al. state that this behavior could be the result of deamidation. FX 629 at 2298. Dr. Strickland did not take this deamidation, or other potential charge modifications to the polypeptide chain, into account when he drew

his conclusions, and no tests were presented to ascertain whether such modifications were present or had taken place. LR '334, 700, 702-703 (Strickland); FR 5312 (Cumming).

B. PROPOSED CONCLUSIONS OF LAW

VI-1. 35 U.S.C. §102(b) provides that a person shall not be entitled to a patent if:

> (b) the invention was patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for the patent in the United States.

Although the person attacking the patentability of a claim carries the burden of persuasion, once a prima facie case of anticipation is made out, the burden shifts to the patentee to produce countervailing evidence. Cable Elect. Products, Inc. v. Genmark, Inc., 770 F.2d 1015, 1022-23 (Fed.Cir. 1985).

VI-2. A movant's burden on issues of patentability is by a "preponderance of the evidence." Decision on Motions dated July 6, 1990, (Paper No. 42). This burden has been likened to the burden on the primary examiner in rejecting claims or on a request for reexamination. Jacobs v. Moriatry, 6 USPQ2d 1799, 1801 (Bd. Pat. App. & Int. 1988). Thus, in assessing the propriety of an examiner's rejection for unpatentability based on obviousness, the Board will "[e]valuate] and [weigh] all the evidence in this case" ... and determine whether "the evidence of obviousness here outweighs the evidence of non-obviousness." Ex parte Beck, 9 USPQ2d 2000, 2002 (Bd. Pat. App. & Int. 1988). See also, Chiong v.

Roland, 17 USPQ2d 1541, 1543 (Bd. Pat. App. & Int. 1990) (the burden of the movant is to establish a prima facie case for obviousness).

VI-3. The Board is not bound by the determination of the primary examiner during ex parte prosecution of the Lin application. Ex parte Meyer, 6 USPQ2d 1966, 1968 (Bd. Pat. App. & Int. 1988) ("we are mindful of our duty to reweigh the entire merits of the application and hence consider all the evidence of record anew"). Accord, Okada v. Hitotsumachi, 16 USPQ2d 1789, 1790-91 (Comm'r. Pat. & Tmks. 1990).

VI-4. For purposes of determining anticipation under 35 U.S.C. § 102(b) "in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification." In re Sneed, 710 F.2d 1544, 218 USPQ 385 (Fed. Cir. 1983). This rule of broadest reasonable construction also applies to patent claims subject to reissue or reexamination. In re Yamamoto, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984).

VI-5. In construing claims, "a court may not redraft a claim for purposes of avoiding a defense of anticipation .... [E]xtraneous limitations the specification .... [should not] be read into the claim wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim ...." Corning Glass Works v. Sumitomo Electric U.S.A, Inc., 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989). E.I. DuPont de Nemours & Co., v. Phillips Petroleum Co., 849 F.2d 1430, 1433,

7 USPQ2d, 1129, 1131 (Fed. Cir. 1988), cert. denied, 488 U.S. 986 (1988).

VI-6. A claim is anticipated under §102(b) "if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference." Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1570, 7 USPQ2d 1957, 1064 (Fed. Cir. 1988), cert. denied, 488 U.S. 892 (1988). Accordingly, it is not material that a prior art reference does not expressly describe a claimed property, if that property is inherent in the anticipating reference. Hughes Aircraft Co. v. United States, 8 USPQ2d 1580, 1583 (Cl. Ct. 1988). ("In these cases, an unstated element that was inherent in the allegedly anticipating reference existed as a matter of scientific fact. It flowed naturally from the elements expressly disclosed in the prior art reference, whether anyone knew it existed or not").

VI-7. All product claims in the Lin application corresponding to the count are product-by-process claims. Paper No. 11 at p. 3. In product-by-process claims, the patentability of the product must be established independently of the process. Scripps Clinic & Research Foundation v. Genentech, Inc., 18 U.S.P.Q.2d 1001, 1016 (Fed. Cir. 1991). In re Brown, 459 F.2d 531, 535, 173, USPQ 685, 688 (CCPA 1972). Accordingly, the "product of the expression in a non-human eucaryotic host cell" limitation in the Lin claims corresponding to the count cannot impart patentability to the Lin claims.

VI-8. The claims of the involved Lin application corresponding to the count, claims 76-83, call for an EPO-like glycoprotein having "an average carbohydrate composition which differs from that of naturally occurring human erythropoietin." The term "average carbohydrate composition" refers to the proportions of the monosaccharide components present in the glycoprotein.

VI-9. The limitation, "average carbohydrate composition which differs from that of naturally occurring human erythropoietin," was relied upon by Lin in the PTO to distinguish the claimed invention over the erythropoietin products of the prior art, including, inter alia, the purified erythropoietin composition disclosed in the Miyake et al. reference.

VI-10. The Miyake et al. reference discloses a purified biologically active erythropoietin product, and a method for obtaining the product from crude urinary source material. Carbohydrate composition analysis for uEPO obtained according to the Miyake et al. (FX 623), and other procedures are set forth in the publications of Dordal et al. (FX 629), Sasaki et al. (FX 626), Takeuchi et al. (FX 625). The published data for the carbohydrate composition of uEPO establishes that there is no statistical difference between the carbohydrate composition of rEPO produced in transfected CHO mammalian cells and uEPO purified from crude urinary sources. Lin has provided no countervailing evidence to the contrary.

VI-11. The recombinant erythropoietin product described in Lin's claim corresponding the count is anticipated by the Miyake et al. reference (FX 623) and the claims corresponding to the count accordingly are unpatentable to Lin under 35 U.S.C. § 102(b).

VI-12. The declaration of Dr. Strickland dated November 30, 1988, submitted in the PTO for the purpose of attempting to establish that rEPO as described in the Lin application has a carbohydrate composition which differs from uEPO, is not probative because it relies on the results of isoelectric focusing experiments which are incapable of indicating any similarity or difference in the average carbohydrate compositions of rEPO and uEPO. The Strickland declaration is also ineffective because Dr. Strickland's methodology in conducting such experiments was fatally defective.

VI-13. As a matter of law, the November 30, 1988 Strickland declaration is ineffective to establish that rEPO has a carbohydrate composition which differs from that of naturally occurring EPO.

VI-14. "To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." Atlas Powder Co., v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Lin application includes only one example of human rEPO for which carbohydrate composition data is set forth. In that example, (Example 10), expression was obtained in a Chinese

hampster ovary ("CHO") cell. Throughout the prosecution of the involved Lin application which resulted in the allowance of the claims corresponding to the count, Lin relied exclusively upon experimental data obtained with samples of human rEPO expressed in CHO cells. There is no evidence of record that the EPO expressed in other non-human eucaryotic cells has an average carbohydrate composition which differs from that of naturally occurring EPO.

VI-15. The evidence establishes that human rEPO obtained from the expression in a CHO host cell of an exogenous DNA sequence encoding human EPO has an average carbohydrate composition which cannot be distinguished from that of naturally occurring human EPO. The Lin patent application contains no disclosure which would enable one of ordinary skill in the art to obtain different types of human rEPO which does differ in its average carbohydrate composition from that of naturally occurring human EPO.

VI-16. Because the rEPO products made in accordance with Lin's application cannot be distinguished from the erythropoietin products of the prior art, (Conclusions of Law VI-7, VI-15, supra.) the Lin claims corresponding to the count are unpatentable to Lin under 35 U.S.C. § 112 (1st para.) for failure to provide an enabling disclosure thereof.