UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, vs. F. HOFFMANN-LA ROCHE LTD; ROCHE DIAGNOSTICS GmbH; and HOFFMANN-LA ROCHE INC. Defendants.	CIVIL ACTION No.: 05-CV-12237WGY

RULE 56.1 STATEMENT OF UNDISPUTED MATERIAL FACTS IN SUPPORT OF ROCHE'S MOTION FOR SUMMARY JUDGMENT THAT CLAIM 7 OF PATENT NO. 5,756,349 IS INVALID UNDER 35 U.S.C. § 112 AND IS NOT INFRINGED

Defendants F. Hoffmann-La Roche Ltd, Roche Diagnostics GmbH, and Hoffmann-La Roche Inc. (collectively, "Roche") submit the following statement of undisputed material facts pursuant to Local Rule 56.1 in support of their motion for summary judgment that claim 7 of the U.S. Patent No. 5,756,349 (the " '349 patent") is invalid and not infringed.

1. Amgen has asserted that that Roche infringes claim 7 of the '349 patent. (Ex. A at 3).[1]

2. Claim 7 states: "A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5**,** or 6**."** (Ex. B at col. 38, ll. 34-36).

[1] "Ex. ___" refers to the exhibits attached to the accompanying Declaration of Howard S. Suh In Support of Roche's Motion for Summary Judgment That Claim 7 of Patent No. 5,756,349 Is Invalid Under 35 U.S.C. § 112 And Is Not Infringed.

3. Claims 1 of the ‘349 patent reads:

> Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.

(Ex. B at col. 38, ll. 8-14).

4. Claim 2 covers “[v]ertebrate cells according to claim 1 capable of producing in excess of 500 U erythropoietin per 10^6 cells in 48 hours.” (Ex. B at col. 38, ll. 15-17).

5. Claim 3 covers “[v]ertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.” (Ex. B at col. 38, ll. 18-20).

6. Amgen alleges that Roche infringes claim 7 by using cells according to claims 1, 2 and 3 of the patent. (Ex. A at 21).

7. Adopting Amgen’s construction, this Court has decided that “human erythropoietin,” in the context of the claims of the patents-in-suit, means “a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine.” (Ex. C at 27:8-10, 39:7-10).

8. Erythropoietin (“EPO”) is generally measured in Units (“U”), which quantify the biological activity of a sample as measured in an *in vivo* bioassay. (*See* Ex. D at 73:8-74:13; Ex. E at 50:20-52:18, 56:1-6; Ex. F at ¶ 34; Ex. G at ¶ 120).

9. The claim limitation “U of erythropoietin” is not defined in the patent. (*See* Ex. B).

10. The standard quantity of measure for Erythropoietin is the Unit (“U”), which quantify the biological activity of a sample as measured in an *in vivo* bioassay. (*See* Ex. D at 73:8-74:13; Ex. E at 50:20-52:18, 56:1-6; Ex. F at ¶ 34; Ex. G at ¶ 120).

11. Radioimmunoassay ("RIA") is a competition binding assay, meaning that it is designed to measure the amount of a protein (such as EPO) in a test sample by quantifying the extent to which the protein in the test sample competes for binding to antibodies that recognize specific portions of EPO with a known amount of radiolabeled protein that can be identified and measured. (Ex. H at ¶ 12).

12. By comparing the assay results with a standard curve generated by testing a series of samples having known concentrations of the protein against the same radiolabeled protein, one can assess how much of the protein was in the unknown sample. (Ex. H at ¶12).

13. RIA cannot directly determine Units of biological activity of a test sample. (Ex. E at 56:7-10; Ex. I at 64:22-65:25; Ex. F at ¶ 51).

14. Antibodies will recognize protein fragments or any molecule that contains the epitope to which it binds. (*See* Ex. J at 151:18-152:8).

15. RIA does not necessarily detect "erythropoietin" in its entirety, and in fact, could recognize "relevant portions" of EPO, including EPO fragments. (Ex. J at 220:4-20).

16. Anti-EPO antibodies "can bind to any epitope that's recognized by that antibody," including EPO fragments. (Ex. J at 151:18-152-8).

17. RIA alone cannot distinguish between "erythropoietin" and EPO fragments. (Ex. E at 49-50).

18. The presence of fragments can result in overestimating "erythropoietin" levels. (Exs. K, L).

19. The '349 patent points out that the Amgen patent application which ultimately issued as U.S. Patent No. 4,558,006 describes "a highly specific monoclonal anti-erythropoietin

antibody which is also specifically immunoreactive with a polypeptide comprising . . . the first twenty amino acid residues of mature human erythropoietin. (Ex. B at col. 8, ll. 48-55).

20. The ‘349 patent describes “monoclonal or polyclonal antibodies” which are immunoreactive with both naturally occurring EPO and “synthetic polypeptides wholly or partially duplicative of continuous sequences of erythropoietin amino acid residues.” (Ex. B at col. 10, ll. 48-62).

21. RIA is used to measure erythropoietin in a sample based on its immunological reactivity with an antibody raised against EPO. (Ex. G at ¶ 48).

22. An EPO RIA cannot distinguish between, for instance, unmodified erythropoietin and erythropoietin that has been desialated and has no in vivo biological activity. (Ex. G at ¶ 48; Ex. J at 133:24-25).

23. RIA is a quantitative measure of native protein structure but not a direct measure of its *in vivo* potency. (Ex. M at AM-ITC 00156691).

24. Since before the time of the invention, the “Unit” of EPO has been understood to be a measure of biological activity of erythropoietin. (Ex. E at 50:20-51:21, 52:7-16, 52:20-54:1, 56:1-6; Ex. F at ¶ 75).

25. Converting the measured amount of protein to “U of erythropoietin” requires reference to a standard. (Ex. H at ¶ 32).

26. There never was a single standard for RIA. (Ex. E at 53:5).

27. Amgen has relied upon different EPO standards for its assays including RIAs. (Ex. I at 45:18-25, 134:9-11; 170:17-171:20; 183:20-184:3; 184:14-185:2).

28. The ‘349 patent does not specify what standard is to be used in the RIA recited in the claims. (Ex. B at col. 16, line 43; Ex. J at 131:10-16).

29. The first international reference standard for erythropoietin was adopted in the 1960's. (Ex. O at AM-ITC 00558662).

30. The second international reference preparation for human erythropoietin was established by the National Institute for Biological Standards and Control (NIBSAC) in 1972. Exs. O, P).

31. The data which determined the second international reference preparation for human erythropoietin clearly showed strong heterogeneity among the various laboratories and assay methodologies. (Ex. O at AM-ITC 00558662; Exs. P, Q).

32. The CAT-1 standard was not calibrated against the second international reference preparation for human erythropoietin. (Ex. Z at AM-ITC 00550542).

33. Amgen used CAT-1, rather than the international standard, in performing the work described in its patents. (Ex. I at 134:9-137:23; 194:7-16).

34. Amgen began using another standard, "Lot 82," made from EPO purified from the urine of a single patient, when the supply of the CAT-1 was exhausted. (Ex. I at 60-61; Ex. R).

35. At least until March 15, 1990, Amgen reported specific activity in arbitrary (Amgen) units rather than International Units. (Ex. T at AM-ITC 00558619).

36. During prosecution of the application that ultimately issued as the '933 patent, the Patent Office rejected a claim to a process for preparing a biologically active glycosylated polypeptide which process included "growing a mammalian host cell which is *capable of* effecting post-translational glycosylation of polypeptides expressed therein." (Ex. W (emphasis added)).

37. Amgen cancelled a pending claim that the Patent Office it considered to be "vague and indefinite in the recitation of 'a host cell capable of effecting post-translational glycosylation of polypeptides.'" (Exs. X, Y).

Dated: June 22, 2007
Boston, Massachusetts

Respectfully submitted,

F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

By its Attorneys,

/s/ Kimberly J. Seluga

Lee Carl Bromberg (BBO# 058480)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
Kimberly J. Seluga (BBO# 667655)
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292
kseluga@bromsun.com

Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky *(pro hac vice)*
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Peter Fratangelo (BBO# 639775)
Vladimir Drozdoff (*pro hac vice*)
David L. Cousineau (*pro hac vice*)
KAYE SCHOLER LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836-8000

CERTIFICATE OF SERVICE

I hereby certify that a redacted version of this document was filed through the ECF system and was sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies were sent to those indicated as non registered participants on June 22, 2007.

/s/ Kregg T. Brooks
Kregg T. Brooks

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