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UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No.: 05-12237 WGY

AMGEN INC.'S RULE 56.1 SEPARATE STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT THAT DR. LIN'S ASSERTED CLAIMS ARE DEFINITE, ADEQUATELY DESCRIBED AND ENABLED

The following facts are beyond genuine dispute and compel summary judgment as a matter of law on Roche's counterclaims of invalidity.[1]

Definiteness

A. "Non-naturally occurring"

1. As affirmed by the Federal Circuit, the term "non-naturally occurring" means a product "not occurring in nature."

- Defs.' Mem. in Opp'n to Amgen Inc.'s Claims Construction Br. (Docket No. 322), App. B at 10.

[1] All citations to numbered exhibits herein refer to exhibits to the Declaration of Renee DuBord Brown in Support of Amgen Inc.'s Motion for Summary Judgment that Dr. Lin's Asserted Claims are Definite, Adequately Described and Enabled.

Dockets.Justia.com

2. As determined by the Federal Circuit, the term "non-naturally occurring" serves as negative source limitation that "merely prevents Amgen from claiming the human EPO produced in the natural course."

- *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) ("[T]he 'non-naturally occurring' limitation . . . merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use negative limitations such as 'non-human' and 'non-natural' to avoid rejection under § 101.")

3. Amgen added "non-naturally occurring" as a "negative limitation" to differentiate Lin's claimed invention from naturally occurring EPO products during patent prosecution.

- Ex. 25, '933 Prosecution History, 12/20/95 Second Preliminary Amendment and Remarks at 6 (AM-ITC 00941549).

4. The specification distinguishes between Lin's claimed recombinantly-produced products and those products that are produced without human intervention.

- Ex. 3, '933 Patent at 8:16-21; 33:39-44.

5. The term "non-naturally occurring," as it pertains to the claimed product, is distinct from the term "human urinary erythropoietin."

- Ex. 3, '933 Patent Cl. 1.

6. Roche did not assert that the term "non-naturally occurring" was indefinite during *Markman*; rather, Roche adopted the Federal Circuit's construction.

- Defs.' Mem. in Opp'n to Amgen, Inc.'s Claims Construction Br. (Docket No. 322), App. B at 10.

B. "***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,"

7. '349 Claim 7 is directed to a process for making erythropoietin by growing vertebrate cells in culture.

- Ex. 5, Cl. 7.

8. According to the language of Claim 7, the cells used in the claimed process must make the recited levels of erythropoietin under the culturing step used by the infringer.

- Ex. 5, Cl. 7 (". . . ***the step of culturing, under suitable nutrient conditions, 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] . . ."). (incorporating Cl. 1, from which it depends).

9. The United States Patent Office has issued over 228,000 patents containing claims that use the term "capable of" and 306 patents containing claims that use the term "capable upon" since 1976.[2]

- Source: www.uspto.gov (June 5, 2007).

10. Roche has been issued claims that have been presumed valid using the term "capable of."

- Ex. 7, U.S. Patent No. 4,353,982 (Claim 1), issued to Defendant Hoffmann-La Roche Inc. and claiming a process for determining the amount of an enzyme, creatine kinase, in a sample by using an antibody "***capable of*** immuno-reactively binding selectively one of the B or M subunits of the creatine kinase in the sample" (emphasis added).

C. "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"***

11. In the 1950's, in order to help standardize the results being reported by various laboratories studying various putative preparations of erythropoietin, a "unit" of erythropoietin activity, based on the observation that cobalt chloride can induce erythropoietin production, was

[2] In particular, see Ex. 7, U.S. Patent No. 4,353,982 Claim 1, issued to Defendant Hoffmann-La Roche Inc. and claiming a process for determining the amount of an enzyme, creatine kinase, in a sample by using an antibody "***capable of*** immuno-reactively binding selectively one or the B or M subunits of the creatine kinase in the sample" (emphasis added).

defined as that amount of erythropoietic activity equivalent to 5 micromoles of cobalt chloride in a test animal.

- Ex. 8, Fried et al., "Studies on Erythropoiesis: III. Factors Controlling Erythropoietin Production," *Proc. Soc. Exp. Biol. Med.* 94:237-41 (1957).
- Ex. 23, 2/14/07 Goldwasser Tr. at 50:20-52:10.

12. As different preparations of EPO became available over the subsequent years, rather than measuring EPO activity using cobalt chloride, an International Reference Preparation (IRP) standard was agreed upon and such standards were administered and distributed, in part, by the World Health Organization.

- Ex. 22, 5/31/07 Goldwasser Tr. at 175:14-17.

13. The unitage for each successive IRP EPO standard was based on the original definition of "unit" and was thus defined indirectly by reference back to the erythropoietic activity of 5 micromoles of cobalt chloride.

- Ex. 16, 5/17/07 McLawhon Tr. at 266:8-267:24.

14. Radioimmunoassays (RIAs), as referenced in the '349 Patent, are used to measure the amount of EPO in a sample with an antibody raised against purified EPO. The results of an RIA to measure EPO are reported in terms of "units" or "mU" of erythropoietin.

- Ex. 9, Egrie et al., "Development of Radioimmunoassays for Human Erythropoietin Using Recombinant Erythropoietin as Tracer and Immunogen," *J. Immunol. Methods,* 99:240 (1987).
- Ex. 10, C. Zaroulis et al., "Serum Concentrations of Erythropoietin Measured by Radioimmunoassay in Hematologic Disorders and Chronic Renal Failure," *Am. J. Hemtol.*, 11:91 (1981) (reporting erythropoietin serum concentrations in mU).

15. The use of an RIA to measure for the presence of EPO was well-known and well-understood by an ordinarily skilled artisan at the time of Dr. Lin's inventions.

- Ex. 11, 5/24/07 Shouval Tr. at 200:2-6.

- Ex. 12, J. Garcia et al., "Radioimmunoassay of Erythropoietin," *Blood Cells*, 5:405-19 (1979).

- Ex. 20, J. Garcia et al., "Radioimmunoassay of Erythropoietin: Circulating Levels in Normal and Polycythemic Human Beings," *J. Lab. Clin. Med.* 99:624-635 (1982).

- Ex. 14, J. Sherwood & E. Goldwasser, "A Radioimmunoassay for Erythropoietin," *Blood*, 54(4):885-93 (1979).

16. Dr. Lin's specification at Example 2, exemplifies the process for conducting an EPO RIA, stating in part:

> Radioimmunoassay procedures applied for quantitative detection of EPO samples were conducted according to the following procedures:
>
> An erythropoietin standard or unknown sample was incubated together with antiserum for two hours at 37° C. After the two hour incubation, the sample tubes were cooled on ice, and ^{125}I-labelled erythropoietin was added, and the tubes were incubated at 0° C for at least 15 more hours. . . .

- Ex. 3, '933 Patent at 16:55-59.

17. An ordinarily skilled artisan would readily understand that he should calibrate the results obtained from the RIA in his laboratory with results obtained using the IRP standard in use at the time.

- Ex. 22, 5/31/07 Goldwasser Tr. at 162:1-24, 163:9-164:11, 179:4-20.

- Ex. 13, Arvind B. Rege, Jesse Brookins & James W. Fisher, "A Radioimmunoassay for Erythropoietin: Serum Levels in Normal Human Subjects and Patients with Hemopoietic Disorders," *J. Lab. Clin. Med.* 100(6):835, fig. 5 (1982) at 840.

- Ex. 14, J. Sherwood & E. Goldwasser, "A Radioimmunoassay for Erythropoietin," *Blood*, 54(4):891, tbl.3 (1979).

18. "Units of erythropoietin . . . as determined by radioimmunoassay" was readily discernible to one of ordinary skill in art in 1983:

- Ex. 11, 5/24/07 Shouval Tr. at 194:17-195:11:

> Q. Now, reading your abstract in 1983, would the person of ordinary skill in the art have been able to understand what was meant with reference to units of erythropoietin as measured by radioimmunoassay?
>
> A. It meant that the cells produced erythropoietin and that it can be measured by radioimmunoassay, which has a standard curve. And there was a reference which was a relative reference which suggests how much -- I mean, which gives you a semi-quantitative idea regarding the units of EPO as decided at that time by those who developed assay.
>
> Q. So is it your view the person of ordinary skill in the art would have understood that language that I just pointed to?
>
> A. Easily.

- Ex. 11, 5/24/07 Shouval Tr. at 198:14-199:10 (term "units per ml of cell culture medium," as measured on RIA, is "self explanatory").

- Ex. 15, 6/8/07 Gaylis Tr. at 273:16-275:12.

- Ex. 16, 5/17/07 McLawhon Tr. at 24:18-26:18.

19. The antibodies used in an RIA can be similarly "calibrated" so that an "apples" to "apples" comparison will be made.

- Ex. 22, 5/31/07 Goldwasser Tr. at 163:9-164:5.

D. "Human erythropoietin"

20. The Court's April 17, 2007 tentative construction for "human erythropoietin" is "a protein having the amino acid sequence of human EPO, ***such as*** the amino acid sequence of EPO isolated from human urine."

- Ex. 1, 4/17/07 *Markman* Hearing Tr. at 23:17-39:10 (emphasis added). The Court took under advisement whether the term should include reference to glycosylation as well as human erythropoietin's amino acid sequence.

21. Roche did not assert that the term "human erythropoietin" was indefinite during the *Markman* proceedings.

- Defs.' Opening Mem. in Supp. of Their Proposed Claim Construction (Docket No. 311) at 6-7.

22. The specification specifically contemplates that "human erythropoietin" may include proteins with an amino acid sequence that corresponds to allelic variants.

- Ex. 3, '933 Patent at 35:17-31.

  > Comprehended by the present invention are those various naturally-occurring allelic forms of EPO which past research into biologically active mammalian polypeptides . . . indicates are likely to exist . . .Allelic forms of mature EPO polypeptides may vary from each other and from the sequences of FIGS. 5 and 6 in terms of length of sequence and/or in terms of deletions, substitutions, insertions or additions of amino acids in the sequence . . . .

- Ex. 3, '933 Patent at 10:8-15.

  > The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.

23. Example 10 of the specification, describing a method for producing "human erythropoietin," discloses products that have a 1-165 amino acid sequence.

- Ex. 19, 9/28/99 Decl. of Jeffrey K. Browne, Ph.D.

Enablement and Written Description

24. Amgen's specification describes and enables one of ordinary skill in the art to make human erythropoietin as claimed in the '933 and '422 Patents.

- *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334-37 (Fed. Cir. 2003).

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Respectfully Submitted,

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By its attorneys,

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