Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 484

IN THE UNITED STATES DISTRICT COURT
FOR THE 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 U.S. District Judge Young

ROCHE'S RULE 56.1 STATEMENT OF UNDISPUTED MATERIAL FACTS IN SUPPORT OF ROCHE'S MOTION FOR SUMMARY JUDGMENT THAT CLAIM 1 OF THE '422 PATENT IS INVALID UNDER 35 U.S.C. § 112

Defendants F. Hoffmann-La Roche LTD, Roche Diagnostics GmbH and Hoffmann-La Roche, Inc. ("Roche") submit the following statement of undisputed material facts pursuant to LR 56.1 in support of their motion for summary judgment that claim 1 of the '422 patent is invalid.

I. Human Erythropoietin

1. Human erythropoietin (EPO) is a glycoprotein hormone in the body that regulates the production of red blood cells. (*See* Ex. 14,[1] Declaration of Harvey F. Lodish, Ph.D. In Support of Amgen Inc.'s Reply to Defendants' Claim Construction Brief filed 3/19/07 ("3/19/07 Lodish Decl."; Docket No. 323) at ¶26); *see also Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1321 (Fed. Cir. 2003) ("EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow.").

[1] "Ex. __" refers to the exhibits attached to the accompanying Declaration of Krista M. Rycroft In Support of Roche's Motion for Summary Judgment That Claim 1 of the '422 Patent Is Invalid Under 35 U.S.C. §112.

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2. Human EPO has a specific 165-amino acid sequence starting with an alanine at the 1 position and ending with aspartic acid at the 165 position. (Ex. 5, Recny *et al.*, "Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin," *J. Biol. Chem.*, 262(35); 17156-17163 (1987); Ex. 14, 3/19/07 Lodish Decl. at ¶27).

II. "Human Erythropoietin" As Disclosed By Lin

3. The '422 patent issued on September 21, 1999 from application Ser. No. 08/100,197 ("the '197 application") filed on August 2, 1993. The '197 application:

> is a continuation of application Ser. No. 07/957,073, filed Oct. 6, 1992, abandoned, which is a continuation of application Ser. No. 07/609,741, filed Nov. 6, 1990, now abandoned, which is a continuation of application Ser. No. 07/113,179, filed Oct. 23, 1987, now U.S. Pat. No. 5,441,868, which is a continuation of application Ser. No. 06/675,298, filed Nov. 30, 1984, now U.S. Pat. No. 4,703,008, which is a continuation in part of application Ser. No. 06/655,841, filed Sep. 28, 1984, now abandoned, which is a continuation in part of application Ser. No. 06/582,185, filed Feb. 21, 1984, now abandoned, which is a continuation in part of application Ser. No. 06/561,024, filed Dec. 13, 1983, now abandoned.

(Ex. 1, '422 patent, Related U.S. Application Data).

4. The '422 patent shares a specification or disclosure with the other Amgen patents-in-suit ("the Lin disclosure"), originating from continuation-in-part application Ser. No. 06/675,298 filed November 30, 1984. *Amgen v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 79 (D. Mass. 2001).

5. Claim 1 of the '422 patent claims: "A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." (Ex. 1, '422 patent, col. 38:37-41).

6. The Court has adopted Amgen's construction of the term "human erythropoietin" to mean "a protein having the amino acid sequence of human EPO, such as the amino acid

sequence of EPO isolated from human urine." (Ex. 3, 4/17/07 Markman Tr. 39:7-10; Ex. 2, Amgen Inc.'s Response to Defendants' Claim Construction Brief filed 3/19/07 ("Amgen's Response Br."; Docket No. 323) at 5).

7. Lin's disclosure expressly acknowledges that at the time the common specification was filed on November 30, 1984 "no substantial amino acid sequence information has been published" for human urinary erythropoietin. (Ex. 1, '422 patent, col. 8:46-49).

8. The Lin disclosure explains to one of skill in the art that "FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues (estimated M.W.=18,399)." (*Id.* at 20:66-21:2; *see also* col. 13:32-34).

9. Similarly, Figure 9 also shows the amino acid sequence of human EPO as 166 amino acids (+1 through +166) and its leader sequence (shown as -27 through -1). (Ex. 1, '422 patent, Figure 9 & col. 19:28-36, 21:2-5, 35:4-11).

10. The Lin disclosure describes only monkey erythropoietin as having 165 amino acids. (Ex. 1, '422 patent at Figure 5 & col: 19:37-40 ("the M.W. of the 165 residues of the polypeptide constituting mature monkey EPO")).

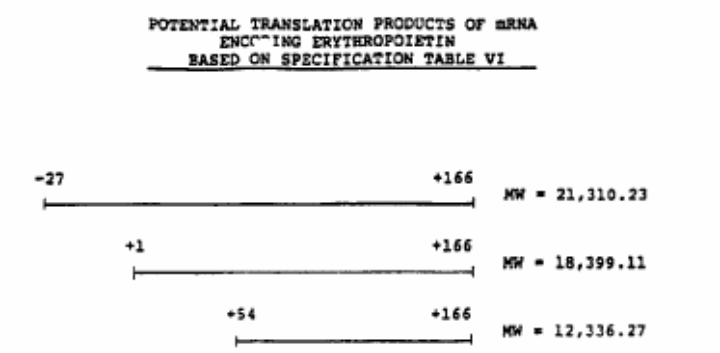
11. Amgen has admitted that, at the time the Lin disclosure was submitted to the Patent Office on November 30, 1984, Lin did not know that human erythropoietin was a protein with a 165 amino acid sequence. (Ex. 6, 12/20/99 Expert Statement of Harvey F. Lodish, Ph.D. at ¶124 ("Although it was not known at the time of the applications for Amgen's Patents were filed, it is no well-understood scientifically that mature human EPO has a 165-amino-acid sequence.")); *see also Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d. 1313, 1343 (Fed. Cir.

2003) ("later research demonstrated that the full sequence of human EPO was actually *165* amino acids").

12. Indeed, on September 27, 1985, Amgen told the U.S. Food and Drug Administration ("FDA") "that the amino acid sequence of natural (urine derived) human erythropoietin and r-HuEPO are identical, and that both conform to the amino acid sequence deduced from DNA sequence analysis of the gHuEPO [genomic human EPO] clone." (Ex. 7, 9/27/85 Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin (r-HuEPO) at AM-ITC 00595293). Figures 4B-6 and 4B-7 submitted to the FDA disclose a 166 amino acid sequence for human EPO. (*Id.* at AM-ITC 00596039-042).

13. Similarly, in 1985, an article co-authored by Lin reported that human EPO was a "166-amino acid mature protein". (Ex. 8, Lin *et al.*, "Cloning and expression of the human erythropoietin gene," *PNAS*, 82; 7580-7584 (1985)).

14. In 1986, during prosecution of a parent application to the '422 patent, Lin argued that there were three potential amino acid sequences for EPO based on Figure 6 — none of which is the 165 amino acid sequence of human EPO now claimed:



(Ex. 9, '298 File History, Paper 12, Ex. 8 of 10/2/86 Amendment and Reply; *see also* Ex. 10, '298 File History, Paper 12, 10/2/86 Amendment and Reply at 35-37).

15. On June 26, 1987 Recny *et al*. submitted a paper that was subsequently published in December 1987, describing the amino acid sequence of human erythropoietin isolated as having a 165 amino acid sequence. (Ex. 5, Recny *et al*., "Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin," *J. Biol. Chem*., 262(35); 17156-17163 (1987) at 17161) ("Our discovery that the natural hormone purified from urine and recombinant hormone purified from CHO cell-conditioned media are both des-Arg^{166} EPO ....)).

III. Amgen Admitted That The Lin Disclosure Lacks Adequate Written Description of a 165 Amino Acid Sequence, Such As the Amino Acid Sequence of EPO Isolated From Human Urine

16. During *Amgen v. HMR/TKT,* Amgen admitted to this Court that:

> When Amgen drafted and filed its patent application, it was unknown and unforeseeable that the human EPO product of example 10 in the patent had 165 amino acids rather than the deduced 166 amino acid sequence shown in Figure 6. Because this fact was not known in 1984 when the written description of Amgen's specification was drafted and submitted, the specification did not expressly recite an EPO having the 1-165 sequence. As explained more fully in Section II(A) below, the absence of an express description of that specific sequence in Amgen's application made a later claim amendment reciting that specific sequence impermisible.

(Ex. 4, Amgen Inc.'s Post-Hearing Memorandum In Support of Its Fed. R. Civ. P. 52(c) Motion That '080 Claims 2-4 Are Infringed Under The Doctrine Of Equivalents filed 8/18/03 ("Amgen's Post-Hearing Memo.") at 1 (AM-ITC 00852563) (emphasis added)).

17. In addition, Amgen admitted that:

> Although then amino acid sequence of 165 human EPO is depicted within the 166 amino acid sequence shown in Figure 6, that fact alone is not sufficient to support a claim that recites the 165 human EPO sequence. Where a specification describes a genus of compounds, such as EPO having the sequence of Figure 6 and fragments thereof, a claim reciting a specific single species within that genus (e.g., 1-165) is not supported unless the specification expressly recites that species as the applicant's invention.

* * *

> Defendants [HMR/TKT] pointed to certain language in Amgen's specification as purportedly providing written support for a claim to 165 human EPO. But the specification only speaks of generic "fragments" of EPO or "DNA sequences encoding part or all of" the EPO sequence. Such reference to a genus of fragments or to DNA sequences of different lengths cannot constitute "blazemarks" pointing to the particular 165 amino acid EPO equivalent in question here, and therefore could not support a claim specifically to such a species.

(Ex. 4, Amgen's Post-Hearing Memo. at 6, 7-8 (AM-ITC 00852568, AM-ITC 00852569-70) (footnotes omitted)).

18. Amgen also admitted that: "Even though 165 human EPO was inherently produced in Example 10, it was not expressly recited as being Amgen's invention in the '080 patent specification." (Ex. 4, Amgen's Post-Hearing Memo. at 6, 7-8 (AM-ITC 00852571)). Because the '422 patent specification shares the same disclosure as the '080 patent, the 165 amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine, also "was not expressly recited as being Amgen's invention" in the '422 patent. *See Amgen v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 79 (each patent-in-suit, including the '422 patent shares a common disclosure and specification).

19. Furthermore, Amgen admitted that: "To subsequently add a description of the later-discovered equivalent — in this case, the fact that the product of example 10 has only, 165 amino acids — would violate the statutory prohibition against adding new matter to the application." (Ex. 7, Amgen's Post-Hearing Memo. at 5 (AM-ITC 00852567)).

20. In *Amgen v. Hoechst Marion Roussel, Inc.*, this Court ruled that: (1) "if, as Amgen suggests, there is new matter to add that is necessary to complete or correct the patent description and protect the invention, the patentee can and should re-file the application" (287 F. Supp. 2d 126, 144 (D. Mass. 2003)) and (2) "Amgen's argument that this [165 amino acid sequence] is new matter suggests that an amendment was not the correct vehicle to make its

desired changes but instead that the more appropriate action would have been for Amgen to have filed a continuation-in-part application." 287 F. Supp. 2d 126, 144 & fn.22 (D. Mass. 2003), *aff'd in relevant part*, 457 F.3d 1293 (Fed. Cir. 2006), *cert. denied*,-- S.Ct. --, 2007 WL 904205 (U.S. May 14, 2007).

IV. The Limitation "Human Erythropoietin " Is Indefinite

21. During the prosecution of the '422 patent, Amgen told the Patent Office that:

> Human erythropoietin as recited in Claim 64 is disclosed in several examples of the application. Example 1 discloses the use of human erythropoietin isolated from the urine of patients afflicted with aplastic anemia ("urinary EPO") to produce tryptic fragments and the amino acid sequencing of those fragments. Examples 7 and 10 disclose the production of human erythropoietin in COS-1 and CHO cells, respectively. Thus, human erythropoietin is understood to include any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in other mammalian cells.

(Ex. 12, '197 File History, Paper 33, 4/28/99 Amendment at 4-5 (emphasis added)).

22. Example 1 of the Lin specification discloses 17 discrete fragments of human urinary erythropoietin that were analyzed for amino acid sequence. (Ex. 1, '422 patent, col. 15:21-53).

23. Lin discloses that two of the 17 fragments, T30 and T38, were "not un ambiguously determined." (Ex. 1, '422 patent, col. 15:28-53).

24. The '422 specification also discloses an amino acid sequence for another fragment, T28, as E-A-I-S-P-P-D-A-A-M-A-A-P-L-R. (Ex. 1, '422 patent, col. 15:47). However, it was subsequently determined by 1985 that the disclosed amino acid sequence for fragment T28 was wrong because of human urinary EPO included a glycosylated serine ("S") instead of the expected methionine ("M") reported in the T28 fragment disclosed by Lin. (Ex. 7, 9/27/85 Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin,

Figure 4B-7 at AM-ITC 00596041-42; AM-ITC 00595293 ("The complete amino acid sequence for human urinary-derived EPO protein in [sic] shown in Figure 4B-7")).

25. A scientific article published by Amgen scientists and Eugene Goldwasser in 1986 also demonstrates that the T28 sequence described in the patent was incorrect. (Ex. 13, Lai *et al.*, "Structural Characterization of Human Erythropoietin," *J. Biol. Chem.*, 261(7); 3116-3121 (1986), Figure 1). This publication, like the sequence submitted to the FDA in 1985, indicates that T28 — including the amino acid in position 126 of human erythropoietin — has a serine and not a methionine as disclosed by the '422 patent.

26. In addition to arguing that "human erythropoietin" has the same amino acid of human EPO such as the sequence of EPO isolated from human urine, Amgen has also relied upon examples 11 and 12 of the '422 patent as defining the claim limitation human erythropoietin to one of ordinary skill in the art. (Ex. 2, Amgen's Response Br. at 7, fns. 22 & 23; Ex. 3 4/17/07 Markman Hearing Tr. 32:15-22).

27. Amgen's expert, Dr. Lodish, admits, however, the products of examples 11 and 12 include "an additional methionine amino acid residue (at position -1)" which is not found in the 165 amino acid sequence of EPO isolated from human urine but, rather, results in a "human erythropoietin" with a 167 amino acid sequence. (*See* Ex. 14, 3/19/07 Lodish Decl. at ¶¶32-33; Ex. *15* 6/4/07 Supplemental Expert Report of Harvey F. Lodish ¶¶ 26-27; Ex. 1, '422 patent, col. 29:42-45).

28. Additionally, example 12 of the '422 patent also purports to describe a human erythropoietin in which the terminal methionone and the initial alanine (at position +1) is not present (Ex. 1, '422 patent, col. 32:10-17). Therefore, while this product of example 12 has a

165 amino acid sequence of +2 through +166, it has a different 165 amino acid sequence than that of EPO isolated from human urine.

29. The Lin disclosure also states that *in vivo* the product of example 12 "differed markedly from the human urinary EPO standard." (Ex. 1, '422 patent, col. 32:22-24).

30. In 1986, Lin argued that there actually were two other amino acid sequences for human erythropoietin (1) a 193 amino acid sequence of -27 to +166 and (2) a 113 amino acid sequence of +54 to +166. (Ex. 12, '298 File History, Paper 12, 10/2/86 Amendment and Reply at 35-37; Ex. 11, '298 File History, Paper 12, Exhibit 8 to 10/2/86 Amendment and Reply).

Dated: June 11, 2007
Boston, Massachusetts

Respectfully submitted,

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