IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC.

Plaintiff,

v.

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

Defendants.

Civil Action No. 05 CV 12237 WGY

U.S. District Judge William G. Young

ORAL ARGUMENT REQUESTED

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

Pursuant to District of Massachusetts Local Rule 56.1, defendants F. Hoffmann-La Roche, Ltd, Roche Diagnostics GmbH, and Hoffmann-La Roche Inc. (collectively "Roche") hereby respond to Amgen's Rule 56.1 Statement of Undisputed Material Facts in Support of its Opposition to Roche's Motion for Summary Judgment that Claim 1 of the '422 Patent is Invalid under 35 U.S.C. § 112.

33. On April 17, 2007, the Court construed "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."

Response to 33: Undisputed. *See also* D.I.# 613 at 15 (July 3, 2007 Claim Construction Memorandum and Order).

34. Throughout his specification, Dr. Lin affirmatively states that the products of his invention include "human erythropoietin" or "human EPO."

Response to 34: Undisputed. Roche does not contest this statement of fact to the extent that Dr. Lin discloses "human erythropoietin" or "human EPO" as having 166 amino acid residues. (*See* D.I.# 485-2 ('422 patent), Figs. 6 and 9).

35. To demonstrate that he in fact possessed "human erythropoietin/human EPO," Dr. Lin's specification offers at least the following evidence regarding the products he obtained:

a. the products were obtained using a DNA sequence encoding human erythropoietin ('933 Patent, at Examples 7, 10, and 11);

b. the N-terminal amino acid sequence of his products corresponds to the N-terminal sequence of human urinary EPO (id. at 28:11-12);

c. the products possess the expected biological activity of human erythropoietin, as measured using a variety of in vivo and in vitro assays (id. at 28:1-10; 28:13-28); and

d. the products of his invention are appropriately glycosylated (id. at 28:1-10; 28:13-28).

Response to 35: Disputed. Dr. Lin did not possess human EPO as now claimed by 165 amino acid residues. Specifically, in response to (b), the specification discloses multiple N-terminal amino acid sequences, including those with an additional initial methionine amino acid residue, and those lacking an initial alanine amino acid residue, which do not correspond to the N-terminal sequence of human urinary EPO. (*See* Amgen's Response to Roche's Statement of Facts ¶ 29).[1] Further, in response to (d), Amgen cannot have it both ways. Amgen has asserted that "human erythropoietin" is a sequence of amino acids, separate from their glycosylation. (*See* D.I.# 613 at 13 (July 3, 2007 Claim Construction Memorandum and Order) (setting forth

[1] Reference is to Amgen's Response to 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 (D.I.# 566).

Amgen's proposed construction: "A protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine.")).

36. Dr. Lin's specification expressly states that "human EPO" is exemplified in Example 10.

Response to 36: <u>Undisputed</u>. Roche does not contest this statement of fact to the extent that the product exemplified in Example 10 is defined by Figure 6, which discloses a 166 amino acid residues. (*See* D.I.# 485-2 ('422 patent), col. 28, lines 26-27).

37. The human erythropoietin produced in Example 10 contains a 1-165 amino acid polypeptide.

Response to 37: <u>Disputed</u>. Recombinant EPO products "purified from mammalian cells grown in culture," including EPO produced Example 10, do not necessarily or inevitably contain a 1-165 amino acid polypeptide. As Dr. Lodish has acknowledged, the terminal arginine amino acid residue at position 166 is not necessarily removed from all secreted forms of erythropoietin:

> A. . . . [T]he majority of the secreted protein is 165. Some of it, I believe, is 166, in at least some people's hands. And that is not uncommon in protein biosynthesis. Processing events may happen; not necessarily be 100 percent.
>
> * * *
>
> Q. . . . I just want to make sure it's right, that with the CHO cell expression of the DNA for human EPO, you will get predominantly EPO that's 1 to 165, but you can get some 1 to 166?
>
> A. I believe that is the case in some experiments.
>
> * * *
>
> A. . . . It would not surprise me that some strains of CHO cells might remove the arginine, and others not.
>
> * * *
>
> Q. Do you know if there are any cells where, when the EPO is purified from mammalian cells grown in culture, it's 1 to 166?

A. My recollection is there are some, and we dealt with it in the TKT litigation. I don't remember the details.

(*See* Ex. 2 (Lodish Depo. Tr. (7/3/07)) at 32-34, 51).[2] Indeed, as initially reported by Amgen scientists, including Dr. Lin, "complete amino acid sequence analysis" of "recombinant EPO produced in cell culture (P.H. Lai, unpubl.)" revealed a "mature hormone [that] is 166 amino acids in length." (Ex. 4 (Browne et al., Erythropoietin: Gene Cloning, Protein Structure, and Biological Properties, Cold Spring Harbor Symp. Quant. Biol. 51: 693-702 (1986) (AM-ITC 00461052-1061) ("Browne 1986")) at 3).

38. Goldwasser's human urinary erythropoietin has the same 165 amino acid sequence as the human EPO product of Example 10.

Response to 38: <u>Disputed</u>. Roche disputes that the sequence of the human EPO product of Example 10 is 165 amino acid residues. (*See supra* Response to 37). Moreover, Roche disputes that the sequence of Goldwasser's human urinary erythropoietin is 165 amino acid residues. When Amgen scientists (together with Dr. Goldwasser) first published the complete amino acid sequence analysis of human urinary EPO, they reported to the scientific community that "[t]he amino acid sequence of human EPO . . . contains 166 residues." (D.I.# 485-20 (Lai et al., Structural Characterization of Human Erythropoietin, J. Biol. Chem. 261:3116-3121 (1986) ("Lai 1986"))). Subsequently, Amgen scientists – including Dr. Lin – published that "[t]he mature hormone is 166 amino acids in length," in view of "complete amino acid sequence analysis of human urinary EPO (Lai et al. 1986) and recombinant EPO produced in cell culture (P.H. Lai, unpubl.)." (*See* Ex. 4 (Browne 1986) at 3).

[2] "Ex. __" refers to the exhibits attached to the Declaration of Krista M. Rycroft in Support of Roche's Reply to Amgen's Opposition to Roche's Motion for Summary Judgment that Claim 1 of the '422 Patent is Invalid under 35 U.S.C. § 112.

Further, a paper published in 1988 by Goto et al. indicated that baby hamster kidney cell-produced EPO – which "retains the carboxy-terminal arginine 166" resulting in a 1-166 amino acid residue product – was "identical to that of u-EPO" as reported in 1986 by Amgen and Dr. Goldwasser. (D.I.# 637-1 (Goto et al., Production of Recombinant Human Erythropoietin in Mammalian Cells: Host Cell Dependency of the Biological Activity of the Cloned Erythropoietin, Nature Biotechnology, 6: 67-71 (1988))).

39. Dr. Lin's specification states that the 166 amino acid sequence disclosed in Dr. Lin's specification is a "deduced" sequence (a sequence derived from the DNA sequence that Dr. Lin had isolated and not from actual sequencing of the entire product).

Response to 39: Undisputed. Roche does not contest this statement of fact but clarifies that to one of skill in the art, Figure 9 discloses human EPO with an arginine as amino acid residue 166, and the DNA sequence that Dr. Lin had isolated refers to Figure 6, which also discloses a 166 amino acid sequence.

40. Example 10 of Dr. Lin's specification inherently yields a 1-165 amino acid product, or that the product's inherent amino acid sequence corresponds to the amino acid sequence of a human urinary EPO preparation.

Response to 40: Disputed. Recombinant EPO products "purified from mammalian cells grown in culture," including EPO produced in accordance with Example 10, do not necessarily, inevitably or "inherently" contain a 1-165 amino acid polypeptide. (*See supra* Response to 37). Furthermore, as noted above, the specification of the Lin patents states that the product of Example 10 corresponds with the sequence in Figure 6. (*See* D.I.# 485-2 ('422 patent), col. 28, lines 26-27).

41. In Amgen's Rule 52(c) motion in the Amgen, Inc. v. Hoechst Marion Roussel, Inc., Civil Action No. 97-10814-WGY (D. Mass. 2001) ("TKT case"), Amgen argued that the Festo presumption against the application of the doctrine of equivalents did not apply to the '080 patent claims.

Response to 41: <u>Undisputed</u>.

42. In that motion, Amgen argued that the written description requirement prevented Amgen from amending its '080 patent claims to recite a hypothetical claim limitation ("human EPO having the specific 1-165 amino acid sequence of Figure. 6."). Amgen's arguments were limited to whether there was support for that hypothetical limitation in a hypothetical claim.

Response to 42: <u>Disputed</u>. Roche contests this statement of fact to the extent that Amgen asserts that its statements regarding the '080 patent would not create any estoppel. By taking the position it did, Amgen unequivocally admitted that the Lin patent specification provides no written description support for a 1-165 amino acid residue human erythropoietin.

43. Amgen's Rule 52(c) Motion explicitly stated that claim 1 of the '422 patent encompassed the 165-amino-acid EPO product, for which there was ample written descriptive support:

> *Defendants argue that Amgen cannot rebut the presumption of estoppel unless it shows that it could not have drafted a claim that encompasses 165 human EPO. As Amgen has explained, the dispositive issue is not whether Amgen could have drafted any claim that would cover 165 human EPO. If that were the dispositive issue, the Federal Circuit would not have remanded the issue of rebuttal for decision by this Court. As this Court previously found and the Federal Circuit affirmed, Amgen drafted another claim that encompasses Defendants' 165 amino acid product (claim 1 of the '422 patent). If the only question was whether Amgen could have drafted a claim that encompassed 165 human EPO, the Federal Circuit would have held that Amgen had already done so in the '422 claim 1 and therefore could not rebut the presumption. (Roche's Br., Ex. 4 at 8-9 (Docket No. 485-7 at 2-3).*

Response to 43: Disputed. Roche disputes this statement of fact to the extent that Amgen's statement is irrelevant. Moreover, "human EPO" was not defined nor at issue during claim construction in *TKT*. (*See Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp.2d 69 (D. Mass. 2001)). Further, "human EPO" was not attacked under 35 U.S.C. § 112 in *TKT*.

44. In an October 2, 1986, Amendment and Reply to a Patent Office action during prosecution of the '422 patent, Amgen argued that Dr. Lin's pending claims were not obvious over the cited prior art.

Response to 44: Undisputed.

45. Amgen's arguments centered on the failed prior-art attempt by Dr. Sylvia Lee-Huang and her colleagues to clone the human EPO gene.

Response to 45: Undisputed.

46. In the action, the Patent Office cited an article by Dr. Lee-Huang and her colleagues in which they suggested that they had cloned the human EPO gene based on the production of translation products (made by translating cDNAs produced from RNA isolated from human kidney tumor tissue) in an in vitro bacterial translation system.

Response to 46: Undisputed.

47. In response, Amgen argued that the DNA sequence described for the first time in Figure 6 of Dr. Lin's patent application, along with computer-assisted modeling, showed that Dr. Lee-Huang and her colleagues could not possibly have cloned the human EPO gene.

Response to 47: Undisputed. Undisputed to the extent that Amgen's statement is irrelevant to the fact that Amgen represented to the Patent Office that human erythropoietin is 166 amino acid residues as a "mature" polypeptide, 193 amino acid residues as a "full-length" polypeptide (with the 27 amino acid residue leader sequence "and a full complement of 166

residues of the mature polypeptide"), and that it potentially could also exist as a 113 amino acid residue polypeptide. (*See* D.I.# 485-17 at 5-7 ('298 File History, Paper 12, 10/2/86 Amendment and Reply at 35-37)). None of these are the 165 amino acid residue sequence of human erythropoietin. (*See* D.I.# 485-9 (Recny et al., "Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin," J. Biol. Chem., 262(35); 17156-17163 (1987) ("Recny 1987"))).

48. Amgen showed that the DNA sequence encoding human EPO described by Dr. Lin in Figure 6 has a limited number of cleavage sites recognized by the restriction enzymes employed by Dr. Lee-Huang to cleave purported cDNA molecules created in her in vitro system, and that none of Dr. Lee-Huang's purported cDNA clones could have been an authentic cDNA encoding the EPO polypeptide.

Response to 48 <u>Undisputed</u>. Undisputed to the extent that Amgen's statement is irrelevant, *see* Response to 47.

49. Amgen argued that Dr. Lee-Huang's "translation products" could not possibly have been authentic human EPO proteins because none of their purported lengths matched the length of a protein that could hypothetically have been produced if an authentic EPO mRNA had been translated in Dr. Lee-Huang's in vitro bacterial translation system.

Response to 49 <u>Undisputed</u>. Undisputed to the extent that Amgen's statement is irrelevant, *see* Response to 47.

50. In Dr. Lin's specification, "erythropoietin" refers to polypeptides having the same sequence of amino acid residues as naturally occurring erythropoietin:

> *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. ('933 Patent, at col. 10:9-15 (emphasis added)).*
>
> *According to the present invention, DNA sequences encoding part or* ***all of the polypeptide sequence of human and monkey species erythropoietin (hereafter, at times, "EPO")*** *have been isolated and characterized. ('933 Patent, at col. 13:50-53 (emphasis added)).*

Response to 50: Disputed. Roche disputes this statement of fact, to the extent that Amgen implies that "erythropoietin" can have "part or all" of the primary structural conformation of human erythropoietin that it disclosed. This Court has already held that Amgen is not entitled to claim "part" of human erythropoietin. (*See* Response to 52). Therefore Amgen can claim no more (and no less) than "all" of the primary structural conformation of human erythropoietin that it disclosed – i.e., human EPO having 166 amino acid residues.

51. The prosecution history of the '422 Patent similarly makes plain that "human erythropoietin" includes any polypeptide that has the same sequence of amino acid residues as EPO isolated from human urine:

> *[H]uman 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. (Roche's Brief, Exh. 12 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33)), at p. 5).*

Response to 51: Disputed. Quoting from the same paragraph:

> 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 in other mammalian cells. ('197 File History, 4/28/99 Amendment (Paper 33) at 4-5 (emphasis added)).

Thus, as the full quote clarifies, the '422 patent prosecution history in fact makes plain that human erythropoietin is understood to have the amino acid residue sequence of the EPO disclosed in Examples 1, 7 and 10. However, like the rest of Dr. Lin's specification, none of these Examples disclose a 165 amino acid residue human erythropoietin. Example 1 does not disclose the full amino acid residue sequence of human erythropoietin, but rather the sequences of EPO fragments which contain mistakes. (*See* D.I.# 485-2 ('422 patent), cols. 15-16). Further, Example 7 fails to disclose any amino acid residue sequence. (*See id*. cols. 22-24). And as noted above, Example 10 discloses a product corresponding to the sequence of Figure 6. (*See id*., col. 28, lines 26-27; *see also* Response to 36).

52. "Human erythropoietin" also includes any naturally occurring allelic variations in the amino acid sequence of human EPO.

Response to 52: <u>Disputed</u>. While Roche does not contest this statement of fact to the extent that the specification of the Lin patents states that Dr. Lin's invention encompasses allelic variations of human erythropoietin, there is only a single purported "allelic variant" disclosed in the specification of the Lin patents, and there is no definite description of any additional allelic variants. (*See infra*, Response to 56).

Moreover, during the prosecution of Application No. 675,298, which is the parent application to all of the patents-in-suit, the Patent office rejected Amgen's claims to DNA sequences "coding for a polypeptide fragment or polypeptide analog of naturally-occurring erythropoietin" as being indefinite in violation of 35 U.S.C. § 112. (*See* D.I.# 637-22 at 2 (November 30, 1984, Appl. No. 06/675,298 at 100); D.I.#637-23 at 4-5 (June 16, 1986 Office Action, 06/675,298-8 at 4-5)).

Amgen eventually cancelled its EPO analog claims in favor of a new narrower claim directed to a sequence encoding a protein "having an amino acid sequence sufficiently duplicative of that of erythropoietin." This narrower claim was held invalid by the Federal Circuit for lack of enablement. (*See Amgen Inc. v. Chugai Pharm. Co*., 927 F.2d 1200, 1214 (Fed. Cir. 1991)). The Federal Circuit there noted that over 3600 different such variants can be made by substituting at only a single amino acid position, and over a million by substituting at only three amino acids. (*Id*. at 1213).

Amgen also surrendered claims to proteins "sufficiently duplicative" of EPO during prosecution of the '933 patent after the PTO rejected them on grounds of nonenablement and indefiniteness. (D.I.# 593-3 ('178 File History, Paper 13, 6/20/89 Office Action) at 3).

53. Roche offered a similar construction for "human erythropoietin" at Markman except that Roche sought to further limit the term by also requiring the presence of particular glycosylation (carbohydrate structures) attached to the amino acid sequence by mammalian cells as of Lin's invention date:

> *a glycoprotein having the amino acid sequence of erythropoietin isolated from human urine having the same structure that would be produced by mammalian cells as of the invention date. (Defs.' Opening Mem. in Supp. of Their Proposed Claim Construction (Docket No. 311), at p. 1).*

Response to 53: <u>Disputed</u>. Roche never advocated a claim construction that defined "human erythropoietin" by its amino acid sequence. Roche took the position that if the term could be defined at all, "it must be amino acid sequence, it must be secondary structure, it must be the tertiary structure, it must have the three-dimensional structure, it must be human EPO." (*See* Ex. 5 (4/17/07 Markman Tr.) at 21-22). At the time, Roche expressly pointed out "the patent is ambiguous because they did not know [the 165 amino acid sequence]." (*Id*. at 21).

54. Roche argued that its proffered definition "was supported by the patentee's definition and use of this term in the specification and the prosecution histories," and was consistent with the understanding of an ordinarily skilled artisan.

Response to 54: Undisputed.

55. *Roche's expert witnesses have acknowledged that human erythropoietin contains the same amino acid sequence as human urinary erythropoietin, which has the 1-165 amino acid sequence*.

Response to 55: Disputed. Roche disputes this statement of fact to the extent that Amgen's statement is irrelevant. Furthermore, the amino acid sequence of human erythropoietin was not determined until after the filing dates of the Lin patents, and was never disclosed. (*See* D.I.# 485-9 (Recny 1987); Ex. 2 (Lodish Depo. Tr. (7/3/07)) at 30).

56. As the specification specifically contemplates, "human erythropoietin" may include proteins with an amino acid sequence that corresponds to allelic variants.

Response to 56: Disputed. While Roche does not contest this statement of fact to the extent that the specification of the Lin patents states that Dr. Lin's invention encompasses allelic variations of human erythropoietin, the specification of the Lin patents purport to identify only a single "allelic variant." (*See* D.I.# 485-2 ('422 patent), col. 21, lines 7-15; *id*. col. 35, lines 26-28). This variant is not a 1-165 amino acid residue erythropoietin.

The Lin patents contain no definite description of other "allelic variants." (*See* D.I.# 485-2 ('422 patent), col. 35, lines 21-26 ("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 acid residues in the sequence, with consequent potential variations in the capacity for glycosylation."); *id*. at col. 35, lines 28-

30 ("naturally-occurring allelic forms of EPO-encoding DNA genomic and cDNA sequences are also ***likely to occur*** . . . .") (emphases added)).

Furthermore, the prosecution and litigation history of the Lin patents establish that Amgen is not entitled to amino acid residue sequences that correspond to allelic variants. (*See* Response to 52).

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

Response to 57: <u>Disputed</u>. *See supra*, Response to 36-40.

Dated: July 9, 2007
Boston, Massachusetts

Respectfully submitted,

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

By their Attorneys,

/s/ Nicole A. Rizzo

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
nrizzo@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 the 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 the above date.

/s/ Nicole A. Rizzo
Nicole A. Rizzo