UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN INC.'S RENEWED MOTION FOR JUDGMENT AS A MATTER OF LAW PURSUANT TO RULE 50(a)

TABLE OF CONTENTS

Page No.

TABLE OF AUTHORITIES

Page No.

Cases

Statutes

I. INTRODUCTION

At the close of evidence of the validity phase of trial, Amgen renews its Motion for Judgment as a Matter of Law pursuant to F.R.Civ.P 50(a). This motion renews in its entirety the motion Amgen filed on September 25, 2007 at the close of defendants' evidence in the validity phase, and Amgen respectfully refers the Court to that motion[1] and the memorandum in support of it.[2]

What follows is a short discussion of the most salient flaws in Roche's case.[3]

II. ROCHE HAS FAILED TO PRESENT EVIDENCE THAT THE PATENT OFFICE DID NOT CONSIDER

Because Roche cannot point to any evidence submitted in support of its invalidity contentions that was not considered by the Patent Office,[4] its burden of proof is "especially difficult." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed Cir. 1990).[5]

III. ROCHE HAS FAILED TO PRESENT A PRIMA FACIE CASE OF OBVIOUSNESS OF THE '422 OR '933 CLAIMS OR OF ANTICIPATION OF THE '933 CLAIMS

A. ROCHE'S PROOF IGNORES THE SOURCE AND PROCESS LIMITATIONS OF THE '422 AND '933 CLAIMS

Roche has failed to present evidence that would establish a *prima facie* case that the

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[1] D.I. 1136.

[2] D.I. 1137-2.

[3] Roche has now narrowed its invalidity allegations to obviousness of all asserted claims; anticipation of '933, claims 3, 7-9 and 12; lack of written description and indefiniteness based on the limitation "human erythropoietin" as to '422, claim 1, '868, claims 1-2, '698, claims 6-9, '349, claim 7; '933, claims 7-9, 11, 12 and 14; and lack of enablement of '349, claim 7. D.I. 1141, pp 1-2. Roche, however, did not offer any expert testimony, through Dr. Flavell or otherwise, as to the lack of written description or indefiniteness based on the "human erythropoietin" limitation with respect to the '868 patent, the '698 patent, or claim 14 of the '933 patent. In view of that, and in view of the fact that Roche abandoned all other previous allegations of invalidity, judgment for Amgen on such allegations is appropriate.

[4] In fact, Roche's expert on obviousness, Dr. Lowe, acknowledged that all of the prior art references he relied on in connection with his obviousness opinions were before the Patent Office. 9/7/07 Trial Tr. 379:9-380:19.

[5] *See also, American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed Cir. 1984).

asserted product and pharmaceutical composition claims of the '422 and '933 patents were obvious at the time of Lin's inventions. Claim 1 of the '422 Patent includes the source limitation "purified from mammalian cells grown in culture." Claims 3, 7-9, 11, 12 and 14 of the '933 patent include the product-by-process limitation: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell…."[6]

Roche does not dispute that Dr. Goldwasser's urinary EPO preparation fails to meet the source limitations of '422 claim 1 or the product-by-process limitations of the '933 claims.[7] Instead, Roche asserts that these source and product-by-process limitations can be disregarded on the premise that they fail to impart any structural or functional difference that distinguishes the claimed products from Goldwasser's urinary EPO preparation. But before Roche can disregard either limitation, it must first prove, by clear and convincing evidence, that these limitations fail to distinguish the prior art. And that, in turn, requires proof, by clear and convincing evidence, that a product identical to a prior art product would in fact be produced from the recited source or by the recited process.[8]

Other than unsubstantiated speculation, Roche offers no proof of that whatsoever. In fact, Roche's expert, Dr. Bertozzi, acknowledged that source limitations ***can*** impart structural differences:

> "Q. Do you agree, Doctor, that glycosylation of a protein which is produced by living tissues on the one hand can differ drastically from the

[6] '933 claim 3 expressly contains that limitation. Claims 7-9, 11, 12 and 14 depend on claim 3 and are thus likewise subject to that limitation.

[7] Roche's Dr. Spinowitz ultimately admitted that Dr. Goldwasser's urinary EPO preparation was not "purified from mammalian cells grown in culture," (9/12/07 Trial Tr. 856:19-21; 873:19-24), and Roche's expert Dr. Bertozzi offered no opinion that Goldwasser's uEPO preparation satisfies the "non-naturally occurring limitation," (9/14/07 Trial Tr. 1007:23-1008:11).

[8] Roche's argument that Lin could not distinguish the product claims in the '933 and '422 patents from the prior art solely on the basis of source or process limitations ignores the applicable law. The Court in *SmithKline v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006) makes clear that process limitations may impart novel structure to a product claim and therefore serve to distinguish a product from the prior art. *See* Amgen's Bench Memorandum Clarifying Case Law Concerning Source and Process Limitations. (D.I. 1237.)

glycosylation of the same protein produced by cells from those same tissues when those cells are grown in culture instead of in a living body?

A. Yes, I would say there could be changes in the sugars. Yes."[9]

Against the background of that admission, Roche's ability to present clear and convincing evidence that a product identical to a prior art product would be produced from the recited source, or by means of the recited process, becomes extraordinarily difficult indeed.

1. Roche Bears The Burden of Proving Invalidity by Clear And Convincing Evidence; It Cannot Shift The Burden to Amgen

Rather than meeting its burden, Roche tries instead to shift the burden to Amgen to prove that the prior art product has a different structure than the claimed products.[10] Such burden shifting as proposed by Roche would, of course, negate the presumption of validity under 35 U.S.C. § 282. The law is clear that a patentee retains its statutory presumption of validity throughout the obviousness determination, and the party asserting invalidity retains the burden of proof by clear and convincing evidence. *See, Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1364 (Fed. Cir. 1998).

In its wrongheaded attempt to shift the burden, Roche relies on *In re Marosi,* 710 F.2d 799 (Fed. Cir. 1983) and *In re Moeller,* 117 F.2d 565 (C.C.P.A. 1941). Both cases involved appeals from decisions of the Board of Appeals of the USPTO, and both held that applicants seeking product-by-process claims bear the burden of proof that they have a concept of a new product which has characteristics that distinguish it from the prior art product. Of course, in that context, before any patent issued and before the presumption of validity applied, the applicant bears the burden of showing that its product is distinct from the prior art. Those cases have no bearing here, where Amgen long ago sustained its burden of proof as an applicant before the patent office, and now enjoys the presumption of validity which Roche has the burden to

[9] 9/14/07 Trial Tr. 1078:10-16.
[10] D.I. 1144.

overcome. Roche's use of the holdings in *Marosi* and *Moeller* to place on Amgen the burden of proving its patents valid is plainly without merit.

2. Roche Also Bears The Burden Of Presenting Corroborated Evidence Of Invalidity

As discussed below, Dr. Bertozzi, on behalf of Roche, offers nothing but uncorroborated and speculative testimony in support of her obviousness opinions. The law requires, however, that oral testimony that is offered by itself to invalidate claims of an issued patent must be corroborated, either by a disinterested witness or by some physical evidence. *Finnigan Corp. v. Int'l. Trade Comm'n.*, 180 F.3d 1354, 1369 (Fed. Cir. 1999) (The law requires "corroboration . . . of any witness whose testimony alone is asserted to invalidate a patent, regardless of his or her level of interest").[11]

The *Finnigan* court indicated that corroboration is required "because of doubts that testimonial evidence alone in the special context of proving patent invalidity can meet the clear and convincing evidentiary standard to invalidate a patent."[12] The Court went on to say: "[t]he law has long looked with disfavor upon invalidating patents on the basis of mere testimonial evidence absent other evidence that corroborates that testimony."[13] In that regard, the requirement of corroboration is a "stringent" one.[14] The rule has been applied to expert as well as fact testimony.[15]

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[11] *See also, Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1217 (Fed. Cir. 2002); *IMX, Inc. v. Lendingtree, LLC*, 405 F.Supp.2d 479 (D. Del. 2005).

[12] *Finnigan Corp.*, 180 F.3d at 1368.

[13] 180 F.3d at 1366. The Federal Circuit noted that while it had in the past applied corroboration requirements more often in the context of priority disputes under §102(g), there was no principled reason for applying a different rule when other subsections of §102 are implicated.

[14] *Juicy Whip, Inc. v. Orange Bang, Inc.*, 292 F.3d 728, 741-43 (Fed. Cir. 2002).

[15] *Neupak, Inc. v. Ideal Mfg. & Sales Corp.*, 168 F.Supp.2d 1012 (D. Minn. 2001); *Stambler v. RSA Security, Inc.*, 243 F.Supp.2d 70 (D. Del. 2003).

B. DR. BERTOZZI'S OPINIONS THAT THE STRUCTURES OF THE GLYCOFORMS IN DR. GOLDWASSER'S URINARY EPO ARE IDENTICAL TO THE STRUCTURES OF ONE OR MORE EMBODIMENTS OF LIN'S CLAIMS—AND THAT SHE COULD ENGINEER AN IDENTICAL EMBODIMENT IF SHE WANTED TO—ARE SPECULATIVE AND UNCORROBORATED

Dr. Bertozzi opined that the mixture of glycoforms in Dr Goldwasser's urinary EPO was the same as the mixture of glycoforms in *some* embodiment of Dr. Lin's claims. However, she offered no evidence that any such embodiment actually existed or what it was. She performed no tests or experiments,[16] and she did not testify as to any prior art reference that supported her opinion that such an embodiment in fact existed.

Indeed, she testified that the structure of Goldwasser's urinary EPO was ***unknown,*** as were the structures of most recombinant EPOs. In response to a question as to whether Dr. Goldwasser's urinary EPO preparation is identical to any recombinant human erythropoietin, she testified:

> "Well, any recombinant erythropoietin, as you phrase it, has not been characterized, so we don't know the structures of any recombinant human erythropoietin explicitly. The only recombinant erythropoietins that have been characterized have been those products made from Chinese hamster ovary cells and purified in a certain way. . . ."[17]

Such testimony effectively disqualified her from clearly and convincingly explaining whether and how the structure of Goldwasser's EPO could possibly be identical to any other EPO product.

As to Dr. Goldwasser's urinary EPO preparation, not only did Dr. Bertozzi present no evidence demonstrating what populations of molecules or structures were actually present in Dr. Goldwasser's EPO, but also she admitted that only some of the glycoforms in that preparation

[16] 9/14/07 Trial Tr. 1066:10-19; 1074:8-15.

[17] 9/14/07 Trial Tr. 1069:25-1070:5.

had been made in mammalian cells.[18]

Finally, the utter flimsiness of Dr. Bertozzi's opinions was brought home when, on ***redirect examination***, she testified for the first time that she had done a "statistical analysis," based on all the data she had reviewed, "to determine the likelihood that the structures from the CHO EPO are the same as those in Goldwasser's EPO . . . ." Based on that analysis, she concluded that "it's statistically impossible not to have the same structures, the structures must be the same, and that's the basis of my opinion."[19] She admitted on re-cross that her "statistical analysis," which, as she said, was the "basis of [her] opinion," was ***not*** in her expert report.[20]

And although she said the structures were the same, Dr. Bertozzi admitted that the proportions of those structures present in the CHO EPO and Goldwasser urinary EPO were different.[21] Further, as Dr. Strickland testified (on deposition) in Roche's case, not all the structures in Goldwasser's urinary EPO are found in recombinant EPO, e.g. different sialic acid linkages.[22]

While Dr. Bertozzi ***talked about*** similarities of the urinary EPO preparation and the claimed products, she was unable to point to any actual recombinant EPO product within the scope of Lin's claims that was identical in structure to the prior art urinary EPO.[23] Attempting to remedy that failure, she testified that she "***could***" engineer forms of recombinant EPO within the scope of Lin's claims that ***would be*** identical to the structures in Goldwasser's urinary EPO

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[18] 9/14/07 Trial Tr. 1129:4-9.

[19] 9/24/07 Trial Tr. 1149:15-1151:1.

[20] 9/14/07 Trial Tr. 1178:20-23.

[21] "What this suggests is that the mixture of glycoforms that Amgen purified from their CHO cells had different relative amounts of glycoforms compared to the mixture that Goldwasser purified from human urine. So in other words, all the data suggests that the structures are the same in the two materials, but that the relative proportions are different. And these data, I would say, concur with that interpretation. So in my opinion, these are evidence that there is a difference in the proportions, yes." 9/14/07 Trial Tr. 1116:10-19.

[22] 9/25/07 Trial Tr. 1376:17-25.

[23] 9/14/07 Trial Tr. 1169:20-1170:14.

preparation.

She was then asked:

> "Q: You have not performed an experiment where you can demonstrate to the jury that you have been able to make a recombinant human EPO that has all of the structures of Goldwasser's urinary EPO, have you?
>
> . . .
>
> A: I have not done that experiment."[24]

She did not explain how, even today, one could produce or select a population of recombinant EPO molecules within the scope of Lin's claims that duplicated the population of molecules that comprised Goldwasser's urinary EPO. Indeed, she admitted that she would have to go outside the Lin patents' teachings to try to accomplish engineering a cell to produce Goldwasser's urinary EPO.[25]

Dr. Bertozzi's naked opinions that the structures of Goldwasser's urinary EPO are identical to those of some embodiment of Lin's claims, and that she could engineer a product within the scope of the claims that would have structures identical to the urinary EPO product, were entirely uncorroborated.[26] Such opinions are precisely the kind of speculative, unsupported, and possibly biased oral testimony, offered as clear and convincing evidence to

[24] 9/14/07 Trial Tr. 1074:8-15. If she could do it, as she says, one wonders why she has not, given Roche's position that the existence of a recombinant EPO within the scope of Lin's claims that has the identical structures of prior art EPO would be invalidating.

[25] 9/14/07 Trial Tr. 1073:14-25.

[26] The other data Dr. Bertozzi referred to during her testimony did not corroborate her opinions. She testified that while she did not perform any tests comparing the prior art urinary EPO with any embodiments of Lin's claims (9/14/07 Trial Tr. 1066:10-19), she reviewed data comparing urinary EPO to recombinant EPO produced in CHO cells. 9/24/07 Trial Tr. 1149:15-1150:15. And while she testified that such tests showed similarities, the fact remains that she testified that certain comparisons between those same two materials showed differences in the glycoform distribution and specific activity. *See* 9/14/07 Trial Tr. 1095:9-1097:21; 1115:7-1116:6; 1116:7-19; TX 2059 at 699, TX 2062 at 247, 249. More importantly, the data she looked at did not corroborate her speculative opinions that Goldwasser's EPO had the identical structures as some undefined embodiments within the scope of Lin's claims, and that one "could" engineer an embodiment within the scope of Lin's claims that would be identical in structure to Goldwasser's urinary EPO.

invalidate an issued patent, which is not appropriate absent corroboration.[27]

It is respectfully submitted that no reasonable jury, applying a clear and convincing standard, could conclude that Roche has presented *prima facie* evidence that a product identical to the Goldwasser prior art urinary EPO would in fact be produced from the source or using the process recited in the '422 and '933 claims.

IV. ROCHE HAS NOT PRESENTED *PRIMA FACIE* EVIDENCE SUFFICIENT TO SHOW THAT LIN'S '868, '933, '698, AND '349 CLAIMS WERE OBVIOUS

To prove obviousness, Roche must demonstrate, by clear and convincing evidence, that the differences between the prior art and Lin's claimed inventions, as defined by all limitations of each claim, are such that the claimed inventions would have been obvious to an ordinarily skilled worker at the time of the invention. *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998). Because Lin's '933, '698, '868 and '349 patent claims all require DNA encoding human EPO,[28] Roche, as a matter of law, has failed to present *prima facie* evidence that the asserted claims were obvious, and judgment as a matter of law should be entered in favor of Amgen on this defense.

A *prima facie* showing of obviousness of a claim reciting a DNA sequence requires a prior art compound structurally similar to the recited DNA, and some suggestion, motivation or reason to modify the structurally similar prior art compound to make the recited DNA. The

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[27] As courts have noted, application of the corroboration requirement does not mean that the witness is not telling the truth or is not credible. Rather, it is a recognition that the statutory presumption of validity, and the accompanying requirement that challenges to the validity of issued patents be supported by clear and convincing evidence, require more than just uncorroborated oral opinions. *Finnigan Corp.*, 180 F.3d at 1370.

[28] '933 independent claim 3 claims "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin. . . ." '868 claim 1 also references "growing mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin . . . ." '698 claim 6 references "growing vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of Figure 6 . . . ." '349 claim 7 which depends on claim 1 references "cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin."

foregoing principle was established in *In re Dillon*, 919 F.2d 688 (Fed Cir. 1990) and *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000). The *Dillon* standard was reaffirmed by the Federal Circuit even after the Supreme Court's decision in *KSR* in *Takeda Chem. Ind. Ltd v. Alphapharm Pty, Ltd*, 492 F.3d 1350 (Fed. Cir. 2007).

A. ROCHE HAS FAILED TO PRESENT ANY EVIDENCE OF EPO-LIKE DNA STRUCTURES IN THE PRIOR ART THAT WOULD RENDER OBVIOUS THE CLAIMS REQUIRING DNA ENCODING HUMAN EPO.

Roche has presented no evidence of a prior art compound that was structurally similar to the EPO DNA. Nor has Roche presented any evidence of any suggestion or motivation to alter any such similar compound to make the claimed EPO DNA sequence.

B. KNOWLEDGE OF AN AMINO ACID SEQUENCE IS NOT SUFFICIENT TO RENDER OBVIOUS THE DNA ENCODING THAT PROTEIN

A DNA molecule cannot be obvious if there is no DNA sequence information available in the prior art. Roche's argument, through its expert Dr. Lowe, that there was some information available as to the amino acid sequence of the EPO protein is irrelevant. A partial amino acid sequence of the protein does not render obvious the nucleotide sequence of the DNA encoding the protein. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995); *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993); *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991); *Takeda Chem. Ind., Ltd. v. Alphapharma Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) *Regents of the Univ. of Cal. v. Monsanto*, 2005 U.S. Dist. LEXIS 40379, *35 (N.D. Cal. Dec. 16, 2005).

C. AN ALLEGED PROCESS OR METHOD TO OBTAIN THE DNA SEQUENCE IS NOT SUFFICIENT TO RENDER OBVIOUS THAT SEQUENCE

Roche's only evidence of the obviousness of the EPO gene sequence was Dr. Lowe's testimony that methods were available in 1983-84 from which one skilled in the art could, with the purified EPO protein in hand, derive the gene sequence. However, the asserted claims require possession of the DNA sequence itself—they are not claims to a method for obtaining the gene sequence. As a result, cloning methods in the prior art cannot, as a matter of law, render a

claim to a DNA sequence obvious. *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995); *In re Bell,* 991 F.2d 781 (Fed. Cir. 1993); *Amgen v. Chugai,* 927 F.2d 1200 (Fed. Cir. 1991).

As the Federal Circuit held in *Amgen v. Chugai*, a research plan for isolating the EPO DNA sequence is insufficient to establish conception of the EPO DNA sequence. In *Amgen* the court held that conception of the EPO DNA sequence could not have occurred until the gene itself was successfully isolated, and for that reason rejected GI's contention that a planned method to clone the gene was sufficient to prove conception.

"What cannot be contemplated or conceived cannot be obvious."[29] And that is why proof of known methods for cloning genes cannot, as a matter of law, establish a *prima facie* case of obviousness of the DNA sequence. *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995); *Mendenhall v. Cedarapids,* 5 F.3d 1557, 1570-71 (Fed. Cir. 1993); *Fiers v. Revel,* 984 F.2d 1164, 1169 (Fed. Cir. 1993); *Amgen v. Chugai,* 927 F.2d 1200 (Fed. Cir. 1991); *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 494 F.Supp.2d 54, 60 (D. Mass. 2007).

V. AMGEN SHOULD HAVE JUDGMENT ON ROCHE'S PRIOR INVENTORSHIP DEFENSE UNDER 35 U.S.C. § 102 (g)

Roche alleges that Dr. Fritsch cloned the EPO gene in July 1984 and expressed EPO in CHO cells in September 1984, before the November 30, 1984 effective filing date of the patents-in-suit. In reprising its allegations regarding prior inventorship under 35 U.S.C. § 102(g), Roche ignores the incontrovertible evidence of record, that it introduced, establishing that Lin isolated the DNA encoding human erythropoietin prior to his December 1983 patent application (Trial Exhibit 2014), and that human erythropoietin was produced in mammalian cells prior to his February 1984 patent application (Trial Exhibit 2015).[30] Dr. Lin's September 1984 patent

[29] *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995).

[30] *See also* Lin and Browne trial testimony: 9/27/07 Trial Tr. 1688:24-1689:2; 9/27/07 Trial Tr. 1688:24-1689:2; 9/27/07 Trial Tr. 1688:24-1689:2; 9/27/07 Trial Tr. 1688:24-1689:2; 9/27/07 Trial Tr. 1688:24-1689:2. 10/1/07 Trial Tr. 1924:20 – 1925:11; 10/1/07 Trial Tr. 1937:7 – 1939:16; Tr. Ex. 2016 pp. 57-58;. Tr. Ex. 2016, p. 20, lines 14-21; Trial Tr. 357:6-11.

application included the production of *in vivo* biologically active human EPO in CHO cells and the amplification of EPO DNA to produce the levels received in the '349 claims.[31]

In contrast, Fritsch's deposition testimony shows only that he cloned the human EPO gene in July 1984 and expressed it in CHO cells in late September 1984. While Fritsch testified that he sent samples out to Dr. Dukes for biological assay results on September 24, 1984, no testimony was presented as to the results of those assays.[32] Similarly, no testimony was presented for dates of work by Fritsch relating to amplification or production of EPO at levels claimed in the '349 patent claims.

Beyond that, of course, Roche seeks to rewrite history. Magistrate Judge Saris in the *Chugai* litigation found that Lin was the first to invent the EPO DNA, and the Board of Patent Appeals and Interferences found that Lin was the prior inventor of the DNA, process and product claims.[33] In contrast to the extensive record examined by the Court in *Chugai* and the Board in the interferences, here, Roche has only presented a few excerpts of Fritsch's deposition – certainly no more and much less than the Court and the PTO Board considered. Given the prior decisions and the incontrovertible evidence in this record, Roche fails to meet its burden in alleging prior inventorship under 35 U.S.C. § 102(g) and Amgen is entitled to judgment on this issue.

[31] Dr. Browne testified that the *in vivo* activity was confirmed in April-May 1984. 10/1/07 Trial Tr. 1937:7-1939:16.

[32] Trial Tr. 357:6-11.

[33] *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1207 (Fed Cir. 1991); *Fritsch, et al. v. Lin*, 1991 W.L. 332569 *3 (B.P.A.I. 1991).

VI. ROCHE HAS FAILED TO MEET ITS BURDEN OF PROVING THAT ANY OF DR. LIN'S ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

A. CLAIM 7 OF THE '349 PATENT IS ENABLED AND ADEQUATELY DESCRIBED

1. The "Vertebrate Cells" Limitation is Not Invalid For Lack of Written Description or Enablement

In both its 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11)[34] and Pre-Trial Brief,[35] Roche alleges that claim 7 of the '349 patent is invalid due to lack of written description and enablement of the claim term "vertebrate cell." At trial, Roche presented no evidence to support these contentions. Amgen is entitled to judgment as a matter of law that claim 7 of the '349 patent is adequately described and enabled with regard to the "vertebrate cells" claim limitation.[36]

2. The Limitation of "U of Erythropoietin per 10^6 Cells in 48 Hours as Determined by Radioimmunoassay" is Not Invalid for Lack of Enablement

On August 27, 2007, the Court issued an order granting Amgen's motion for summary judgment that the '349 claim, as to the limitation "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay," was definite. Among the bases for Roche's assertions that the '349 claims were invalid was the allegation that one of ordinary skill in the art would be unable to distinguish between "fragments" and full length human EPO, thus making it impossible to standardize results.[37]

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[34] Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11) at p. 12.

[35] D.I. 919 at pp. 50-52.

[36] In its interrogatory responses, Roche also alleged that '349 claim 7 was invalid for failure to enable or describe the full scope of the limitation "transcription control sequence," as it appears in the claims on which claim 7 depends. Having failed to raise these arguments in its August 31, 2007 Pre-Trial Brief (D.I. 919) and at trial, Amgen assumes that Roche has withdrawn any invalidity argument related to the term "transcription control sequences" as well.

[37] *See e.g.* Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11) at p. 16.

Having lost this issue on summary judgment, Roche is now seeking to re-package its "fragments" attack in the guise of non-enablement allegations. To support its argument that the limitation "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay" is not enabled, Roche offers only the testimony of its expert Richard Flavell. Even with his testimony, a reasonable jury could only reach one conclusion – that one of ordinary skill in the art could conduct a radioimmunoassay without undue experimentation to determine whether or not he was falling within the scope of '349 claim 7.

As Roche's expert Dr. Edward Harlow testified to by video deposition at trial, one of skill in the art would have known how to perform a radioimmunoassay to detect the amount of EPO being produced by vertebrate cells:

> Q. Now, radioimmunoassay techniques can be used to detect protein antigen if a suitable antibody is available, correct?
>
> A. Yes.
>
> Q. **And as of December 1983 as ordinarily skilled artisan would have known how to use a radioimmunoassay to measure the amount of protein antigen in a solution, correct?**
>
> A. **That's correct**.[38]

Dr. Lowe similarly testified, opining that a radioimmunoassay is "a standard laboratory technique."[39]

In contrast to the testimony of Roche's Drs. Harlow and Lowe, Dr. Flavell offered an enablement opinion based on the sole ground that a person of skill in the art could not have known how to use radioimmunoassay because one would not be able to determine whether he

[38] 9/28/07 Trial Tr. 1799:3-10. *See also* 9/28/07 Trial Tr. 1800:9-13; 1798:16-1799:2 (providing that Dr. Harlow's expertise extends to radioimmunoassay techniques).

[39] 9/6/07 Trial Tr. 304:20-23. Similarly, Roche's expert Dr. Kadesch testified before the Court during arguments on the ODP issue that RIA was a standard assay used in 1983 or 1984 to measure the amount of protein, and that one of skill in the art would have certainly known about the RIA assay. 10/1/07 Trial Tr. 12:4-13:3 (afternoon session).

was detecting a full length protein or a fragment of the protein.[40] In support of this assertion, Dr. Flavell relies only on a review article by Drs. Eugene Goldwasser and Judith Sherwood (TX 2073) that references the presence of EPO fragments in the blood of patients suffering from anemia associated with chronic renal disease.[41]

Dr. Flavell's reliance on TX 2073 is not reasonable. The reference to EPO fragments was made in the context of proteins found in the sera of chronic renal disease patients, ***not*** whether EPO fragments are found in the culture media of vertebrate cells that have been recombinantly engineered to produce human EPO. More importantly, Dr. Flavell ignored the fact that the reference also states that the presence of any fragments can be accounted for by separating out such fragments using known techniques,[42] and the deposition testimony offered by Roche at trial of Dr. Joan Egrie that Amgen used Western analysis to account for fragments.[43] Dr. Flavell also ignored the fact that the publication itself characterized the development of an RIA for EPO as "easy" with the advent of human EPO's "purification" six years before the earliest filing date of Dr. Lin's applications.[44]

Dr. Flavell's cursory opinion, unsupported by any credible evidence, in combination with the admissions of the other Roche witness testimony offered at trial does not meet Roche's burden to prove non-enablement by clear and convincing evidence. Consequently, Amgen is entitled to judgment as a matter of law that claim 7 of the '349 patent is enabled.

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[40] Dr. Flavell's testimony is set forth at 9/24/08 Trial Tr. 1255:15-1273:16.

[41] TX 2073 at 360; 9/24/07 Trial Tr. 1270:3-1273:17.

[42] TX 2073 at 360 ("These small fragments can be separated by gel permeation chromatography").

[43] 9/24/07 Trial Tr. 1184:6-14.

[44] TX 2073 at 359 ("Once the purification of human erythropoietin was complete (Miyake *et al*, 1977) ***it was relatively easy to develop an RIA*** . . .")(emphasis added).

B. THE '422 AND '933 PATENT CLAIMS HAVING THE "PHARMACEUTICAL COMPOSITION" LIMITATION ARE NOT INVALID FOR LACK OF ENABLEMENT

At trial, Dr. Flavell offered his cursory opinion that none of the patents contain any disclosure which one of skill could use on their own to purify EPO protein to achieve the degree of homogenous, contaminant-free protein necessary to make a pharmaceutical composition.[45]

Dr. Flavell's opinion was directed only to his opinion that Amgen's process for purifying its commercial EPO product, as set forth in Amgen's FDA application and a separate Amgen patent, was not set forth in Dr. Lin's patent.[46] This fact has nothing to do with whether Dr. Lin's disclosed process purifies EPO sufficiently for use as a pharmaceutical. More compelling was the admission by Dr. Lowe, Roche's expert on the issue of obviousness, that it would have been obvious to purify recombinant EPO for use as a pharmaceutical composition once such recombinant EPO became available.[47]

Because Roche has failed to carry its burden of establishing lack of enablement by clear and convincing evidence, Amgen is entitled to judgment as a matter of law that claim 1 of the '422 patent and claims of the '933 patent (claims 9, 11, 12, and 14) are enabled. Apparently recognizing that, Roche, based on its previous opposition to Amgen's motion for judgment as a matter of law, has abandoned claims of lack of enablement as to these patents.[48]

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[45] 9/24/07 Trial Tr. 1248:3-1250:12; 9/25/07 Trial Tr. 1359:3-1362:2. Dr. Flavell's opinion regarding the non-enablement of purification of a "pharmaceutical composition" relate to '933 claims 9, 11, 12, and 14, and '422 claim 1.

[46] *See generally id.*; 9/24/07 Trial Tr. 1248:3-1250:12.

[47] 9/6/07 Trial Tr. 303:10-304:1.

[48] D.I. 1141.

C. DR. LIN'S SPECIFICATION ADEQUATELY DESCRIBES AND MAKES DEFINITE "HUMAN ERYTHROPOIETIN"

Dr. Flavell was the sole witness offered by Roche to meet its burden to prove by clear and convincing evidence that the term "human erythropoietin," as construed by the Court, was indefinite or not described. Dr. Flavell's testimony was not directed to either the asserted claims of the '698 or '868 patent, and these claims should stand free and clear of any § 112 attack by Roche.

As to the claims of the '933 patent and '422 claim 1 (and improperly to '349 claim 7), Dr. Flavell's testimony was based upon a further misconstruction of the Court's claim construction for "human erythropoietin" and concluded that it ***must*** mean 165 amino acids.[49] According to Dr. Flavell, because Dr. Lin did not literally state that his product was 165, it was both inadequately described and indefinite.[50] This testimony is insufficient because it misapplies the Court's claim construction and conflates the description and definiteness requirements.

The Court's construction of "human erythropoietin" states: "a protein having the amino acid sequence of human EPO such as the amino acid sequence of EPO isolated from human urine." The definition does not specify 165 amino acids, and Dr. Flavell cites to nothing in the prior art or Dr. Lin's patent that would so limit the definition. Rather, Dr. Lin clearly describes "human erythropoietin" as the product of the expression of the human EPO gene in mammalian cells. In Example 10, Dr. Lin repeatedly refers to the expression product as "human EPO."[51] This description satisfies the requirements of § 112 and comports with the Court's claim

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[49] 9/24/07 Trial Tr. 1242:9-10 ("And what – as we've just discussed, human erythropoietin is defined as 165 amino acids.").

[50] In a throw-away sentence, Dr. Flavell offered the opinion that "allelic variant" could include numerous EPOs but did not support this opinion with any evidence that such multitude actually exists or that one of ordinary skill in the art would be confused about what "human erythropoietin" is. *See* 9/24/07 Trial Tr. 1244:24-1245:3.

[51] 9/24/07 Trial Tr. 99:20-25; 9/5/07 Trial Tr. 116 (Roche's counsel acknowledging that EPOGEN is a 165 amino acid product).

construction.

Even assuming for purposes of this motion that Dr. Flavell's limited reading of the Court's construction is correct, Roche has failed to establish by clear and convincing evidence that Dr. Lin's specification does not describe or render definite a 165 amino acid human erythropoietin product. Neither Dr. Flavell nor any Roche witness has offered the opinion that the product of Example 10 is not comprised of 165 amino acids.[52] Indeed, as Dr. Flavell and Roche's counsel have both acknowledged, one of skill in the art now knows human EPO, including Amgen's commercial product EPOGEN,® to be a 165 amino acid product.[53] As such, no reasonable jury, applying the law of inherency (as it relates to the written description requirement of § 112), could find "human erythropoietin" not adequately described.[54]

Regarding definiteness, Dr. Flavell's opinion is based on his perfunctory conclusion that one of ordinary skill in the art would not know whether human erythropoietin is 165 or 166 and whether an allelic variant of human erythropoietin would be covered by the claim limitation "human erythropoietin."[55] But that position does not render the claims indefinite—it could include both 165 and 166. As for allelic variants, as Dr. Lin's patent describes them, these are naturally occurring variations in the EPO DNA sequence and one example is given in the patent.[56] Dr. Flavell did not identify any other naturally occurring allelic variant.

The Federal Circuit has held that terms may be considered definite where persons skilled

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[52] Dr. Lin's patents make plain that the product of the expression of the human EPO gene in a mammalian host cell as described in Example 10 is "human EPO." *See e.g.*, Exhibit 1, col. 26:4-6; 26:11-15; 26:46-51; 27:46-50; 28:1-5; 28:8-10.

[53] 9/24/07 Trial Tr. 99:20-25; 9/5/07 Trial Tr. 116 (Roche's counsel acknowledging that EPOGEN is a 165 amino acid product).

[54] *Regents of the Univ. of New Mexico v. Knight*, 321 F.3d 1111 (Fed. Cir. 2003); *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419 (Fed. Cir. 1987).

[55] 9/24/07 Trial Tr. 1244:24-1245:3 ("For example, there's discussion of allelic variance in the patent but it doesn't tell us which ones there are. And I don't know if I had a particular allelic variant whether it would be covered or not").

[56] Exhibit 1, col. 35 17-39.

in the art could readily determine the bounds of the claims experimentally.[57] In other words, patent law does not necessarily require patentees to give hard and fast quantitative boundaries to their claims; all that it requires is that the patent "sufficiently informs one of ordinary skill in this art of the boundaries of the claims."[58]

VII. CONCLUSION

For the reasons stated, Amgen's Renewed Motion for Judgment as a Matter of Law should be granted.

[57] *E.g.*, *LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc*., 275 F.3d 1347, 1359-60 (Fed. Cir. 2001) (affirming JMOL that term "substantially completely wetted" was definite where degree was defined functionally (i.e., sufficient to produce X) and readily ascertainable by routine testing).

[58] *Id.* at 1360.

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Respectfully Submitted,

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