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

SUPPLEMENTAL DIRECTED VERDICT OPPOSITION REGARDING STRUCTURAL IDENTITY BETWEEN AMGEN'S PRODUCT CLAIMS AND THE PRIOR ART AS RAISED BY AMGEN DURING SEPTEMBER 24 HEARING

I. INTRODUCTION

Defendants Hoffmann-La Roche, Ltd, Roche Diagnostics, GmbH, and Hoffmann-La Roche Inc. ("Roche") submit this supplemental memorandum in further opposition to Amgen's directed verdict motion on invalidity in order to address certain issues raised by Amgen at oral argument with respect to the Roche's defenses that asserted claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent and claim 1 of the '422 patent are anticipated and obvious.

Counsel for Amgen made the factually and legally misleading argument that Roche's evidence regarding the invalidity of the asserted claims introduced through Dr. Bertozzi's testimony was "insufficient in order to come forward with a prima facie case of obviousness" because of a purported "acknowledgement that the evidence establishes that the one commercial embodiment that exists that [Dr. Bertozzi] compared has a different distribution of glycoforms." (Tr. 9/24/07 at 1316). In fact, the evidence is overwhelming that the asserted claims of the '422 patent and the '933 patent are anticipated and/or made obvious because they do not require products that are functionally or structurally distinct from pharmaceutical compositions comprising human EPO in the prior art.

II. The Structures of Amgen's Claimed EPO Glycoproteins Do Not Distinguish Them From Prior Art EPO

Claim 3 of the '933 patent, from which all asserted claims of the '933 depend, and claim 1 of the '422 patent are claims to products, albeit with the respective source or process limitations, "product of the expression ... in a mammalian host cell" and "purified from mammalian cells grown in culture." However, such limitations do not distinguish these product claims over the prior art because the source or process limitations do not impart "material structural and functional characteristics" unique to the claimed products in comparison with the prior art. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1580,

1584 (Fed. Cir. 1991); *see also SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006).[1] Thus claim 1 of the '422 patent and claims 3, 7, 8, 9 and 11 of the '933 patent read on the prior art structures. Without conferring unique structural features the source and process limitations of the claims cannot make the claims patentable. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003). ("We note that in remand when considering obviousness and anticipation issues relating to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations.").

The evidence of record clearly and convincingly establishes that the source and process limitations of the '933 and '422 patents do not confer any structural or functional features that render the claims novel and non-obvious over human EPO that was purified and isolated in the prior art such as Dr. Goldwasser's EPO. As Dr. Bertozzi testified, relying on data published by and provided to the FDA by Amgen, "[N]othing distinguishes them. The EPO that comes from mammalian cells in culture is *the same*, the molecules are *the same* as Goldwasser's EPO." (Bertozzi 988:19-21 (emphasis added); *see also* Bertozzi 1027:20-1028:2, 1028:15-18). Amgen's own PLA and published articles confirm Dr. Bertozzi's opinions. (Bertozzi 1032:5-1034:17, 1036:20-1037:1, 1041:24-1047:22; TRX 2056-2062).

Amgen now bears the burden of coming forward with evidence that the prior art EPO has a different structure than the claimed product. *In re Marosi*, 218 U.S.P.Q. 289, 293 (Fed. Cir. 1983); *In re Moeller*, 117 F.2d 565, 567 (C.C.P.A. 1941). Indeed, were the law otherwise, a patentee could claim a product made by a particular process without identifying any unique structural features imparted by such a process and then put the onus on all potential infringers to

[1] *See* Roche Motions in Limine D.I. 1047 and 1046; *see also* Exhibit C for relevant statements of law on source and process limitations.

rebut the existence of any and all hypothetical distinctions. Thus, if a process limitation is to impart novel structural limitations to a claim the distinguishing features must be evident in the patent specification or claims.

As reflected in the comments by Amgen's counsel at oral argument, however, Amgen attempts to distinguish the products of the claims over the prior art by relying on purported structural features that are nowhere to be found in its patents. Amgen's counsel even concedes that the boundaries of these putative structural features are unknown, arguing that Amgen's claimed products are heterogeneous mixtures "that vary from composition to composition." (Tr. 9/24/07 at 1312). Yet, Amgen's patents do not define any particular carbohydrate structural features, or secondary or tertiary structural features that distinguish the claimed EPO products from the prior art. Nor are Amgen's claims of the '422 patent and '933 patents limited by any particular distribution of glycoproteins, because glycoform distribution is the result of the particular method of purification used to select a population of glycoproteins. Similarly, the claims are not limited to any level of specific activity which results from selecting a population of glycoforms. Yet, at the hearing, Amgen still argued that alleged differences observed between one population of EPO molecules which is an alleged embodiment[2] of the claims and the prior art EPO demonstrates that the product claims are novel. (Tr. 9/24/07 at 1313:16-20). Thus, Amgen proffers a legally improper test in which novelty of the full scope of an extremely broad claim could be established by a comparison to an unclaimed feature of a single embodiment.

As set forth below, the evidence introduced by Dr. Bertozzi that human EPO glycoproteins from mammalian cells grown in culture are identical to prior art human EPO

[2] Amgen argues that comparisons of prior art EPO to its commercial Epogen product are relevant. Apart from the impropriety of focusing the analysis on comparison of an embodiment to the prior art rather than the claims to the prior art, there is also no evidence at all in the present record that Epogen is actually an embodiment of any of the patents-in-suit. What the evidence does establish is that Epogen is purified according to a method not disclosed in the patents.

according to all of the available characterization techniques, and certainly by the criteria set forth in the patent, are more than sufficient evidence for a reasonable jury to conclude that Amgen's product claims are anticipated and/or obvious. (*Id.*). The evidence also clearly and convincingly shows that the pharmaceutical composition claims and the method claims of the '933 and '422 patents do not add any distinguishing features over the prior art and are invalid.

III. All of the Features of Amgen's '933 and '422 Claims Are Met By Prior Art EPO Glycoproteins and Their Prior Use

Amgen's asserted claims of the '933 and '422 patents fall into three general classes 1) product by process claims: claims 3, 7 and 8 of the '933 patent; 2) pharmaceutical composition claims: claims 9 and 11 of the '933 patent and claim 1 of the '422 patent and 3) method of treatment claims: claims 12 and 14 of the '933 patent.

There is ample evidence in the present record to allow a reasonable jury to find all of these claims invalid as anticipated and/or obvious in view of the prior art teachings of purified human EPO. The 1977 paper by Dr. Goldwasser and Dr. Miyake describes human EPO purified according to a seven step procedure with an *in vivo* biological activity of ~123,000 u/A. (TRX 2002). This material was formulated into a composition including a phosphate buffer and injected into mice and rats. Amgen has admitted that the material caused hemoglobin synthesis in the tested mice.

Claim 3 of the '933 patent recites non-naturally occurring human EPO glycoprotein products made in mammalian host cells that possess the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. Claim 7 of the '933 patent depends from claim 3 with the further limitation that the host cell is a non-human mammalian cell. Claim 8 of the '933 patent depends from claim 3 with the further limitation that the host cell is a CHO cell. Despite Amgen's argument that these claims require a particular

amount of EPO this clear language of the claims does not. Rather, the molecules must only posses an inherent property.

Although the human EPO described by Miyake and Goldwasser was not actually the product of expression in a mammalian host cell as set forth in the '933 patent, the structures of EPO described in the prior art have all of the same physical and chemical properties as a product of that process. Dr. Bertozzi relied on admissions by Amgen in its FDA documents and scientific publications to show that the human EPO described by Miyake and Goldwasser did not occur in nature, by virtue of its isolation and purification, but had the same structure and function as a product produced by the recited process. (Bertozzi 1018:10-1019:5). For instance, Dr. Bertozzi testified that a product made by a mammalian host cell would have the same molecular size, molecular charge, carbohydrate composition and carbohydrate arrangement. (Bertozzi 1027:20-1028:18, 1033:21-1034:17). Amgen's patents disclose no other tests that would allow one to distinguish the products of mammalian host cells from the Miyake and Goldwasser EPO. Thus, claims 3, 7 and 8 of the '933 patent are invalid as anticipated in view of the prior art teaching of the Miyake and Goldwasser 1977 paper.

Claim 1 of the '422 patent recites a pharmaceutical composition comprising a therapeutically effective amount of human EPO and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein the human EPO is purified from mammalian cells grown in culture. Claims 9 and 11 of the '933 patent recite pharmaceutical compositions comprising an amount of a glycoprotein product of, respectively, claims 3 and 7 of the '933 patent, effective for erythropoietin therapy and a pharmaceutically acceptable diluent, adjuvant or carrier.

Clear and convincing evidence also establishes that the pharmaceutical compositions recited in claims 9 and 11 of the '933 patent and claim1 of the '422 patent are anticipated and/or

rendered obvious by Miyake 1977 (TRX 2002; Bertozzi 1018:8-15, 1048:2-1050:7, 1052:14-1053:12) and also by pharmaceutical compositions comprising the EPO described in Miyake used in clinical studies conducted by Dr. Goldwasser and Dr. Baron to treat human anemia patients.[3] Evidence provided by Dr. Bertozzi demonstrates that the structures of the human EPO glycoproteins isolated by Dr. Goldwasser and Dr. Miyake are indistinguishable from EPO made in mammalian host cells according to the '933 patent and human EPO purified from mammalian cells grown in culture according to the '422 patent. (Bertozzi 1018:10-1019:5, 1027:20-1028:18, 1033:21-1034:17). Drs. Bertozzi and Spinowitz also testified, and documentary evidence shows that Dr. Goldwasser's EPO was formulated into a pharmaceutical composition in a therapeutically effective amount as required by claim 1 of the '422 patent and an amount effective for therapy as required by claims 9 and 11 of the '933 patent. (Bertozzi 1055:9-19, 1020:1-5). The Miyake 1977 reference and the Baron-Goldwasser study disclosed pharmaceutical compositions in which Dr. Goldwasser's purified human EPO was incorporated with a pharmaceutically acceptable diluent, adjuvant or carrier, as required by claim 1 of the '422 patent and 9 and 11 of the '933 patent, and was administered in therapeutically effective amounts. (Bertozzi 1006:25-1007:6; 9/11/07, Tr. 718:5-22; 719:5-720:14). Amgen admits (s*ee* RFA 32) that EPO of the Miyake paper increased hemoglobin synthesis in mice. (Bertozzi 1006:25-1007:6). The Baron-Goldwasser study also demonstrated the administration of Dr. Goldwasser's urinary EPO to human patients with the observed erythropoietic effects of increasing nucleated red blood cells, reticulocytes and iron uptake.[4] (Spinowitz 718:5-22, 719:5-720:14).

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[3] *See* Opposition to Amgen's Motion for Judgment as a Matter of Law Regarding Roche's Invalidity Defenses.

[4] See previous footnote.

Claims 11 and 14 of the '933 patent claim a method of treating a kidney dialysis patient which comprises administering a pharmaceutical composition of, respectively, claim 9 and 12, in an amount effective to increase the hematocrit level of said patient. At least one kidney dialysis patient had an increase in hematocrit levels upon administration of Goldwasser's EPO, anticipating Amgen's claims.

Moreover, clear and convincing documentary evidence and expert testimony by Drs. Spinowitz and Bertozzi demonstrate that the methods of claims 11 and 14 of the '933 patent are obvious in light of the prior art disclosures by Miyake 1977 and the Baron-Goldwasser clinical trial in combination with other publications by Essers; Eschbach; and Dr. Goldwasser that provided the motivation to take the pharmaceutical compositions containing the EPO glycoproteins claimed in the '933 and the '422 patents and use them to treat kidney dialysis patients in order to obtain a therapeutic benefit such as increased hematocrit levels. (Bertozzi 1053:13-1055:19). The prior art taught that no inhibitors existed that would prevent treatment by administrations of exogenous EPO protein. Indeed, Dr. Lin's patents note this motivation in the prior art and provide no description themselves of a particular method of administration, thus underscoring the obviousness of using the pharmaceutical compositions for their widely understood purpose. *See, e.g.,* '933 patent (TRX 1), col. 6:41-43.

IV. Amgen's Reliance on Purported Differences Between Particular Embodiments And the Prior Art Based on Structural Characteristics Not Found in the Patents Does Not Overcome the Evidence of Invalidity

Amgen challenges the invalidity evidence noted above with respect to the claims of the '422 and '933 patents solely by arguing that the source and process limitations of the asserted claims impart unique structure. However, Amgen's arguments are all unavailing because they rely on purported differences observed only in certain recombinant EPO compositions to which Amgen's claims are *not* limited. Amgen's claims are directed to any EPO glycoproteins that can

be produced in any mammalian host cells, under any conditions, in any populations, with any specific activity and purified in any way. Thus, Amgen's claim that differences exist with respect to a certain purification of a commercial recombinant EPO and the prior art EPO are irrelevant. Indeed, even this distinction is not meaningful. Dr. Bertozzi's testimony of September 24 demonstrated that different lots of recombinant EPO submitted for regulatory approval by Amgen have a range of specific activity that spans the reported specific activity for Miyake and Goldwasser's EPO glycoproteins. (Bertozzi 1159:1-1161:2). Thus, any supposed difference in specific activity is illusory. Moreover, Amgen has offered no evidence of what Epogen is, let alone that it is covered by these claims. It is a matter of record that the lots submitted for FDA approval were not purified by a method described by the Lin patents. In any case, the proper analysis is a comparison of the full scope of Amgen's claims in the '933 and the '422 to the prior art. Hence, Amgen's reliance on the comparison of an alleged single embodiment to Dr. Goldwasser's prior art EPO is irrelevant.

The purported structural differences cited by Amgen to challenge Dr. Bertozzi's testimony are also inapposite. None of these structural and functional features are described anywhere in the patents nor do they limit the scope of the claims in any way. For instance, in Amgen's Opposition to Roche's Motions *in Limine* regarding the source and process limitations in the '422 and the '933, Amgen refers to various structural features of "Dr. Lin's recombinant EPO" including differences in the proportions of N-linked carbohydrates, differences in the distribution of glycoforms, differences in conformation structures and the functional feature of different specific activity. (D.I. 1101, p. 1). These features are not limitations of the claims and the claimed glycoprotein products include a range of proportions of N-linked structures, glycoform distributions, conformation structures and as is demonstrated by Amgen's PLA

specific activity. The asserted claims are much broader than a single embodiment. It was Amgen's choice to claim so broadly. That a particular composition of the claims, which Amgen's counsel describes as covering varying heterogeneous mixtures, differs from the prior art EPO does not confer novelty to the claims. Indeed, the ranges of possible features within embodiments of the claims demonstrates the breadth of the claims.

Having claimed a vast range of products, Amgen's claims have also swept within their scope the prior art EPO glycoproteins which have been shown to be identical to particular EPO glycoproteins made in mammalian host cells. This identity of structure is well documented in this case by Dr. Bertozzi's testimony and Amgen's own data in its regulatory filings and scientific papers. From this evidence, a reasonable jury could well conclude that the human EPO glycoproteins of the claims of the '422 and '933 patents are not novel and unobvious.

Amgen's argument that there must be contemporaneous recognition in the prior art that Dr. Goldwasser's human EPO has the same structure as an embodiment of the claim is not supported by the law. Whatever physical properties Dr. Goldwasser's EPO possessed are inherent in the structures. For a prior art product to anticipate a later product claim the inherent features of prior art do not have to be recognized under the current view of the law. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). Moreover, an inherent property found in the prior art can be combined with other are to render claimed subject matter obvious. *See In re Schreiber*, 128 F.3d 1473, 1478-79 (Fed. Cir. 1997).

Dr. Bertozzi testified based on objective scientific evidence, that there is a "statistical certainty that the molecules [of the prior art EPO and the molecules claimed by the '933 and '422 patents] have the same structure." (Bertozzi 1146:23-24). Moreover, she considered and applied all the criteria thus set forth in the patents.

In sum, Amgen's attempt to distinguish the products of the claim "inventions" based on unclaimed and unproved structural differences supposedly imparted by the source and process limitations of the claims is utterly without merit.

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