UNITED STATES DISTRICT COURT
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-12237WGY ORAL ARGUMENT SET FOR JULY 17, 2007

DEFENDANTS' REPLY MEMORANDUM IN FURTHER SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT THAT THE ASSERTED CLAIMS OF THE '933 PATENT ARE INVALID FOR INDEFINITENESS AND LACK OF WRITTEN DESCRIPTION

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TABLE OF CONTENTS

Page

INTRODUCTION 1

ARGUMENT 3

A. The Term Non-Naturally Occurring Was Added To The Claims Of The '933 Patent To Overcome Prior Art 3

B. The Claimed EPO Products Had To Be Structurally Distinct To Overcome The Examiner's Prior Art Rejection 6

C. Amgen Distinguishes The EPO Of The Claims Based Only On Glycosylation 6

D. A Mere Source Limitation Would Not Allow One Of Skill In The Art To Distinguish The Glycoproteins Of The Claims 9

E. The Asserted Claims Of The '933 Patent Lack The Written Description Required Under § 112 10

CONCLUSION 10

TABLE OF AUTHORITIES

Page(s)

CASES

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
126 F. Supp. 2d 69 (D. Mass 2001) 7, 8

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
314 F.3d 1313 (Fed. Cir. 2003) 5, 7, 8

Chiron Corp. v. Genentech, Inc.,
2002 U.S. Dist. LEXIS 19150 (E.D. Cal. 2002) 9

General Elec. Co. v. Wabash Appliance Corp.,
304 U.S. 364 (1938) 6

Oakley, Inc. v. Sunglass Hut, Int'l,
316 F.3d 1331 (Fed. Cir. 2003) 9

Schering Corp. v. Geneva Pharm., 339 F.3d 1373 (Fed. Cir. 2003) 5

SmithKline Beecham Corp. v. Apotex Corp.,
439 F.3d 1312 (Fed. Cir. 2006) 6

STATUTES

35 U.S.C. §§ 101 ..... 1, 5

35 U.S.C. § 102(b) 3

35 U.S.C. § 103 3

35 U.S.C. § 112 ..... 1, 10

Defendants F. Hoffmann-La Roche Ltd, Roche Diagnostics GmbH and Hoffmann-La Roche Inc. (collectively "Roche") submit this reply memorandum in further support of their motion for summary judgment that claims 3, 7, 8, 9, 11, 12 and 14 of U.S. Patent No. 5,547,933 (the '933 patent) are invalid under 35 U.S.C. § 112 because they are indefinite or violate the written description requirement.

INTRODUCTION

Amgen's answering memorandum amounts to nothing more than obfuscation. Amgen argues that the claim term "non-naturally occurring" -- which this Court construed to mean "not occurring in nature" -- is not indefinite because, for purposes of 35 U.S.C. §§ 101 (subject matter patentability) and 112 (definiteness), the term does not have to impart any structural identity to the "human erythropoietin glycoprotein" of the claims in order for the claimed invention to be patentable. Thus, according to Amgen, the term "non-naturally occurring" is purely a source limitation that does not distinguish prior art structures. However, the prosecution history of the '933 patent makes crystal clear that the term "non-naturally occurring" was added to the claims of the '933 patent, for purposes of § 102, to overcome prior art. As the applicant stated at the time: "Applicant's incorporation of 'non-naturally occurring' in all independent claims operates to distinguish the subject matter claimed from all prior art reference relating to erythropoietin isolates." (Declaration of Keith E. Toms, Ex. 1, Ser. No. 487,774, Paper 50, December 20, 1995 Second Preliminary Amendment and Remarks at 7).[1] Moreover, Amgen concedes that the meaning of a claim term is the same "whether one is assessing the language for definiteness, subject-matter patentability, or novelty." (Amgen Inc.'s Memorandum of Law in Opposition to

[1] All Exhibits cited herein are attached to the Declaration of Keith E. Toms in Support of Defendants' Reply Memorandum in Further Support of Defendants' Motion for Summary Judgment That the Asserted Claims of the '933 Patent are Invalid for Indefiniteness and Lack of Written Description ("Toms Decl."), dated July 9, 2007.

Defendants' Motion for Summary Judgment That the Asserted Claims of the '933 Patent are Invalid for Indefiniteness and Lack of Written Description) (D.N. 580) at 7 n. 26.)

Yet, Amgen does not and cannot dispute the showing in Roche's opening brief that source alone would not make a non-naturally occurring human erythropoietin glycoprotein patentably distinct from the structures of naturally occurring erythropoietin that constitute prior art to Dr. Lin. Given that the term "non-naturally occurring" was added to the claims of the '933 patent to overcome prior art, the term had to connote a physical difference between the structures of the erythropoietin glycoproteins of the claims (which allegedly do not occur in nature) and the structures of the erythropoietin glycoproteins of the prior art which do occur in nature. The claims are indefinite because whatever structural limitation is imparted by the term "non-naturally occurring" would not allow one of skill in the art to distinguish between the erythropoietin glycoproteins within the claim and those outside of the claim. "Glycosylation" has already been held an indefinite basis for distinguishing the non-naturally occurring glycoproteins of the claims from the naturally occurring glycoproteins found in human urine of the prior art, and the '933 patent mentions no other physical distinction that would be imparted by the claim term "non-naturally occurring."

Amgen is misleading in asserting that "[o]ne of ordinary skill in the art can readily determine whether an accused glycoprotein product was obtained from a natural or non-natural source." (D.N. 580 at 9.) Indeed, Amgen's simplistic solution is that "[i]f the material was obtained from a source that naturally contains EPO without human intervention, it is outside the bounds of the claim. If not, it will be within the scope of the claim if all other limitations are met." (*Id*.) While the manufacturer of the product would know the source, a user -- who is also a potential infringer -- would have no way of knowing whether a particular glycoprotein

infringes or not absent some discernible physical difference between non-naturally occurring EPO of the claims and non-naturally occurring EPO. Amgen has no right through its product claims to block a competitor from making a structure that is identical to a structure that occurs in nature, regardless of the process, yet Amgen's interpretation of the claims seeks to do just that. Furthermore, if the term "non-naturally occurring" imparts structure to distinguish the claimed EPO from the EPO of the prior art, then the "non-naturally occurring" erythropoietin glycoproteins of the claims cannot be distinguished on the basis of source alone. The claims are indefinite in that they disclose no basis for distinguishing the EPO of the patent from the EPO of the prior art.

Finally, if the asserted claims of the '933 patent are read, as they must be, to recite a non-naturally occurring EPO glycoprotein that is physically distinct from naturally occurring EPO, the patent does not teach, per the written description requirement of § 112, that the inventor had possession of the invention of the claims. Given the variability of naturally occurring EPO, Dr. Lin's manufacturing process alone does not teach whether the EPO described in the patent is distinguishable from the prior art. Hence, the asserted claims of the '933 should be invalidated on both indefiniteness and written description grounds.

ARGUMENT

A. The Term Non-Naturally Occurring Was Added To The Claims Of The '933 Patent To Overcome Prior Art

It cannot reasonably be disputed that the term "non-naturally occurring" was added to the claims of the '933 patent to overcome prior art.

In a May 15, 1993 office action, during the '933 patent prosecution, the examiner rejected claims, under 35 U.S.C. § 102(b) or, alternatively, § 103, stating: "No evidence of any difference between the products of the references and the products embraced by the claims is

presented." (Toms Decl., Ex. 2, Ser. No. 202,874, Paper 43, 5/15/95 Office Action at 5.) Following an October 18, 1995 office interview, the applicant added claims, similar to those that had been rejected in view of the prior art, adding the term "non-naturally occurring." (Toms Decl., Ex. 1 at 2.) The Applicant stated: "Applicant's incorporation of 'non-naturally occurring' in all independent claims *operates to* distinguish the subject matter claimed from all prior art reference relating to erythropoietin isolates (Chiba *et al*., Miyake *et al*., Espada *et al*., and Papayannopoulou *et al*.)." (*Id*. at 7 (emphasis added).) The applicant's use of the words "operates to" in characterizing the term "non-naturally occurring" underscores that the term "non-naturally occurring" was intended to impart -- in the words of the examiner -- a "difference between the product of the references and the products embraced by the claims."

The statement on the preceding page of the '933 patent file history -- which Amgen cites (D.N. 580 at 13) -- does not prove that, in the context of claim 3, the term "non-naturally occurring" cured an indefiniteness problem. The applicant stated: "At the interview it was agreed that the negative limitation 'non-naturally occurring" would, when combined with the notation of glycosylation differences in prior claims 87 and 99 (corresponding to new claims 100 and 105) meet Section 112 specificity requirements. All of independent claims 100-105 are similarly limited." (Toms Decl., Ex. 1 at 6.) Although application claim 102 -- now claim 3 of the '933 patent -- did not have the "notation of glycosylation differences" which appeared in application claims 87/100 (issued claim 1) and 99/105 (corresponds to issued claim 6), the examiner's statement that "[a]ll of independent claims 100-105 are similarly limited" suggests that the examiner understood all the claims to draw the same physical distinction between the claimed EPO products and naturally occurring EPO. In any event, this Court and the Federal

Circuit held claims 1 and 2 of the '933 patent invalid for indefiniteness. Thus, the term "non-naturally occurring" was hardly a cure for the 112 rejections.[2]

Also, Amgen's argument that the term "non-naturally occurring" was added for purposes of patentability under § 101 is disingenuous and has no support in the file history. (*See* D.N. 580 at 6-7. There was no § 101 rejection pending when Amgen added the term. (*See* Toms Decl., Ex. 2.)

Further support that "non-naturally occurring" was used in the prosecution to import a physical difference between prior art structures and claimed structures is found by inspecting claim 3 of the '080 patent. (*See* Declaration of Howard S. Suh in Support of Roche's Motion for Summary Judgment That the Asserted Claims of the '933 Patent are Invalid for Indefiniteness and Lack of Written Description (D.N. 507), Exhibit 2, U.S. Patent No. 5,621,080.) That claim has no requirement for a mammalian host cell, and it can not be disputed that naturally occurring EPO structures existed in the prior art with the amino acid sequence of Figure 6. Therefore, if "non-naturally occurring" does not import a structural limitation to this claim, the claim would be invalid for inherent anticipation. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Since Amgen asserted claim 3 of the '080 patent against Roche, it cannot now contend the claim is invalid.

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[2] Claim 3 of the '933 patent -- which does not use the term "having glycosylation which differs from that of human urinary erythropoietin" -- differs from claims 1 and 2 in describing the claimed glycoprotein as a "product of the expression in a mammalian host cell of an exogenous DNA sequence." In the context of the '422 patent, Amgen has taken the position that the similar term -- "purified from mammalian cells grown in culture" "recites the source from which the 'human erythropoietin' component of the claimed composition may be obtained and necessarily imparts a further structural requirement that the product also be glycosylated." Amgen Inc.'s Claim Construction Brief (D.N. 312) at 17. As demonstrated in Roche's pending Motion for Summary Judgment that Claim 1 of U.S. Patent No. 5,995,422 Is Invalid for Indefiniteness and Lack of Written Description, the term "product of the expression in a mammalian host cell" is similarly indefinite to the extent it imparts structural distinction.

B. The Claimed EPO Products Had To Be Structurally Distinct To Overcome The Examiner's Prior Art Rejection

Amgen argues that the term "non-naturally occurring" did not have to be a structural limitation for purposes of §§ 101 and 112 but does not dispute that, for purposes of § 102, a source limitation alone will not distinguish over a prior art product which is otherwise identical. As Roche has already shown, in *Amgen Inc. v. Hoechst Marion Roussel, Inc*. 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003), ("*Amgen II*") the Federal Circuit stated 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." *See also General Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938) ("a patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced"); *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 n.7 (Fed. Cir. 2006) ("a prior art disclosure of a product precludes a future claim to that same product, even if it is made by an allegedly novel process").

Given that the term "non-naturally occurring" was expressly added to the claims of the '933 patent to distinguish the claimed EPO products over prior art EPO products, the term "non-naturally occurring" must refer to glycoproteins "not occurring in nature" which are structurally different from EPO glycoproteins which do occur in nature.

C. Amgen Distinguishes The EPO Of The Claims Based Only On Glycosylation

Contrary to Amgen's assertions, Roche does not contend that the term "non-naturally occurring" means "having glycosylation which differs from that of human urinary erythropoietin." Rather, Roche's position is that (1) the term "non-naturally occurring" had to impart a structural distinction in order to overcome prior art; and (2) that in doing so, the term "non-naturally occurring" makes the claims indefinite because the claims do not allow one of

skill in the art to determine whether any particular erythropoietin is within the claims or outside the claims. The problem for Amgen is that the only physical distinction between the EPO of the claims and the EPO of the prior art recited in the '933 patent is glycosylation. However, that distinction has already been held to be indefinite given that the glycosylation of naturally occurring EPO varies and that the patent does not identify a particular naturally occurring EPO to serve as a basis for comparison.

As explained in Roche's opening brief, glycosylation is the only physical distinction between the non-naturally occurring EPO of the claims and naturally occurring EPO structures of the prior art discussed in the patent specification. (*See* Memorandum of Law in Support of Defendants' Motion for Summary Judgment That the Asserted Claims of the '933 Patent are Invalid for Indefiniteness and Lack of Written Description) (D.N. 506) at 9-10). The '933 patent states that the non-naturally occurring products of the patent have "an average carbohydrate composition which differs from that of naturally-occurring erythropoietin." (*See* D.N. 507, Ex. A, '933 patent, col. 29:5-7).

Roche has also shown that *if* the structural aspect imparted by the term non-naturally occurring is glycosylation, then the claim is indefinite. (D.N. 506 at 14-15). In holding claims which distinguished non-naturally occurring EPO from naturally occurring EPO indefinite, this Court described the glycosylation of naturally occurring EPO as a "moving target" and, therefore, a "standardless standard." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 129, 155, (D. Mass 2001) (*Amgen I*). The Court stated: "[A] definitive comparison is rendered impossible by the fact that human urinary erythropoietin itself varies significantly. This is not the kind of particular pointing out and distinct claiming that is required by the statute. *Id.* at 156. The Federal Circuit agreed: "By definition, one must know what the glycosylation of

uEPO [EPO isolated from human urine] is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO." *Amgen II*, 314 F.3d at 1341.

Amgen mischaracterizes Roche's position as to the application of collateral estoppel here. Roche does not suggest that the courts held in the *HMR/TKT* litigation that the term "non-naturally occurring" is indefinite. Roche maintains only that Amgen is foreclosed, under the doctrine of collateral estoppel, from arguing that the structural distinction imparted by the term "non-naturally occurring" is glycosylation because the issue has already been litigated and glycosylation was held an indefinite basis for distinguishing the products of the claims.[3] *Amgen I* at 156-57; *Amgen II* at 1342. Thus, Amgen is estopped from rearguing -- as it attempts here in citing Dr. Varki's opinion (D.N. 580 at 13) -- whether glycosylation is a definite basis for distinguishing naturally occurring EPO and non-naturally occurring EPO.

Amgen does cite a number of other supposed differences between recombinant and urinary erythropoietin. (D.N. 580 at 12). However, Amgen relies on "a paper published in 1997," which was after the June 1995 actual filing date of the application for the '933 patent and long after the 1984 purported priority date of the '933 patent. In any event, the '933 patent makes no mention of those differences which thus could not have been imparted by the term "non-naturally occurring."[4]

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[3] Roche notes that, before the Federal Circuit, Amgen relied on the argument that the only difference between '933 patent claim 3 and '933 patent claim 1 (which was found indefinite) was that claim 3 recited an exogenous DNA sequence. *See Amgen II* at 1326 ("Unasserted claim 3 of the '933 patent, for example, is virtually identical to claim 1, save for the express limitation regarding the use of 'exogenous DNA'").

[4] If these are true physical distinctions that limit the claim, Amgen will have the burden of proving them in its infringement case, although it makes no attempts to do that in its summary judgment for infringement. (*See* Amgen Inc.'s Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 (D.N. 510)).

D. A Mere Source Limitation Would Not Allow One Of Skill In The Art To Distinguish The Glycoproteins Of The Claims

Amgen insists that non-naturally occurring is a pure source limitation that would nevertheless allow one of skill in the art to "readily determine whether an accused glycoprotein product was obtained from a natural or non-natural source." (D.N. 580 at 9). According to Amgen, "ordinarily skilled artisans . . . need only ask themselves, 'where did this product come from?'" (*Id*.) All that is required is "an alleged infringer's knowledge of where he obtained his product." (*Id*. at 9-10).

Plainly, the inquiry is not that simple. The claim only satisfies § 112 if it defines the product such that "interested members of the public . . . can determine whether or not they infringe." *Oakley, Inc. v. Sunglass Hut, Int'l*, 316 F.3d 1331, 1340 (Fed. Cir. 2003). While the manufacturer of an EPO product knows how it was made, the user of an EPO product does not.

Moreover, if the term "non-naturally occurring" is understood, for purposes of overcoming prior art, to incorporate into the claims of the '933 patent a structural distinction between the claimed products and the products of the prior art, then the claims do not cover non-naturally occurring EPO that is otherwise indistinguishable physically to a naturally occurring EPO. Stated otherwise, the source cannot be the full extent of the distinction. Consequently, the potential infringer cannot determine whether a given EPO product infringes merely by determining the source.

Finally, the fact that this Court was able to construe the term "non-naturally occurring" to mean "not occurring in nature" does not end the indefiniteness inquiry. Indeed, the meaning of the claim term "having glycosylation which differs from that of human urinary erythropoietin" is clear. Nonetheless, that term was held indefinite as used in claims 1 and 2 of the '933 patent to distinguish between non-naturally occurring and naturally occurring EPO. *See also Chiron*

Corp. v. Genentech, Inc., 2002 U.S. Dist. LEXIS 19150 *6 (E.D. Cal. 2002) ("it is not uncommon for courts to find a claim term invalid for indefiniteness after construing the term").

E. The Asserted Claims Of The '933 Patent Lack The Written Description Required Under § 112

There is no merit to Amgen's argument that the claims of the '933 meet the written description requirement because the '933 patent specification shows that Dr. Lin obtained the claimed erythropoietin from a source that does not occur in nature. If, as explained above, "non-naturally occurring" is understood to serve, in the claims of the '933 patent, not purely as a source limitation but also to impart structural identity, then the specification does not show that Dr. Lin was in possession of EPO that was physically distinct from naturally occurring EPO. If the structure of naturally occurring EPO is variable and thus uncertain, as this Court and the Federal Circuit concluded, then the '933 patent does not make clear that Dr. Lin invented EPO that is defined as being different from naturally occurring EPO.

CONCLUSION

For all of the foregoing reasons, this Court should grant summary judgment in Roche's favor holding all of the claims of the '933 patent that Amgen has asserted in this action invalid, under 35 U.S.C. § 112, for indefiniteness and lack of written description.

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Boston, Massachusetts

Respectfully submitted,

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