UNITED STATES DISTRICT COURT
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

AMGEN INC.'S REPLY IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT THAT DR. LIN'S ASSERTED CLAIMS ARE DEFINITE, ADEQUATELY DESCRIBED, AND ENABLED

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I. INTRODUCTION

Amgen's motion for summary judgment of validity under § 112 seeks, in part, judgment that the terms "non-naturally occurring," "U of erythropoietin . . . as determined by radioimmunoassay," "capable of/upon," and "human erythropoietin" are definite. Roche does not dispute the facts alleged by Amgen in support of its motion, agreeing that there are no material issues of fact that would preclude determination as a matter of law whether these claim limitations satisfy the definiteness requirement of section 112.[1]

Instead, Roche's opposition only highlights the many inconsistencies that permeate its case. For example:

(1) ***Non-naturally occurring.*** In opposition to Amgen's motion for summary judgment of no obviousness type double patenting, Roche acknowledges that Amgen added the limitation "non-naturally occurring" to exclude any "EPO polypeptide [that] could not be isolated from natural sources,"[2] but here Roche argues that Amgen added the limitation to exclude products having the same glycosylation as human urinary EPO.[3]

(2) ***"U of erythropoietin . . . as determined by radioimmunoassay."*** In support of its obviousness arguments, Roche proffers expert opinions that certain prior art cells purportedly produced EPO based on radioimmunoassay measurements,[4] but here Roche argues that skilled artisans would not know how to perform radioimmunoassay measurements for the presence of EPO.[5]

(3) ***"Capable of/upon."*** In Roche's motion for summary judgment of no infringement of '349 claim 7, Roche argues that Amgen's proof is insufficient to

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[1] Roche's Opposition to Amgen's 6/20/07 Motion for Summary Judgment That Dr. Lin's Asserted Claims Are Definite, Adequately Described And Enabled (Docket No. 630) (hereinafter "Roche's Opp.") at 1

[2] Roche's 6/29/07 Opposition To Amgen Inc.'s Motion for Summary Judgment of No Obviousness-Type Double Patenting (Docket No. 568) at 7.

[3] Roche Opp. at 5-6.

[4] *See e.g.* 6/20/07 DuBord-Brown Declaration in Support Of Amgen's Motion for Summary Judgment of That Dr. Lin's Asserted Claims Are Definite, Adequately Described and Enabled (Docket No. 534) at Ex. 11 (5/24/07 Shouval Tr. at 194:17-195:11); *id* at 198:14-199:10 (term "units per ml of cell culture medium," as measured by RIA, is "self explanatory"); Docket No. 534 at Ex. 15 (6/8/07 Gaylis Tr. at 273:16-275:12).

[5] Roche Opp. at 12-14.

establish infringement of '349 claim 7 because the cell culture conditions used in Amgen's experiments differed from those used by Roche in its commercial manufacturing process.[6] But here Roche argues that "claim 7 covers production of 'erythropoietin' without regard to how much EPO is actually being made."[7]

(4) ***"Human erythropoietin."*** In its opposition to Amgen's motion for summary judgment of infringement, Roche argues that Lin defined "human EPO" to have a specific meaning that Roche does not infringe,[8] but here Roche argues that the meaning of "human erythropoietin" is unintelligibly ambiguous.[9]

To mask these inconsistencies, Roche's Opposition, like the corresponding four Roche motions for summary judgment to which it refers, is a study in misdirection.

First, Roche directs the Court's attention to its past findings regarding unrelated limitations in claims that are not at issue in this litigation. In so doing, Roche ignores that the limitations actually at issue in *this* case were previously found, either expressly or implicitly, to be sufficiently definite, described, and enabled to result in a finding that the claims that contain these limitations were valid and/or infringed. For example, relying on the Court's past finding that the term "glycosylation which differs from that of human urinary erythropoietin" in '933 claim 1 is indefinite, Roche baldly asserts that the "non-naturally occurring" limitation in the claims at issue here must also be indefinite. But unlike the reference to urinary EPO that was previously found to be indefinite, the intrinsic record shows that "non-naturally occurring" is a negative source limitation that distinguishes Lin's claimed product based on the source from which it is obtained, not a comparison of Lin's claimed EPO with other EPOs.

Roche's arguments regarding "human erythropoietin" similarly ignore the Court's claim construction, past findings, and the intrinsic record. Instead, Roche launches a diversionary

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[6] Roche's 6/22/07 Memorandum In Support of Its Motion for Summary Judgment that Claim 7 of Patent No. 5,756,349 Is Invalid Under 35 U.S.C. § 112 And Is Not Infringed (Docket No. 539) at 19-20.

[7] Roche Opp. at 14.

[8] Defendants' 6/29/07 Opposition to Amgen's Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6 (Docket No. 588) at 3-4.

attack on Dr. Lin's specification that fails to consider either the claim at issue or the specification as a whole.

Regarding the limitations "capable upon/of" and "U of erythropoietin . . . as determined by radioimmunoassay," Roche mischaracterizes both the claim language and the relevant state of the art. Roche also fails to rebut or distinguish the testimony of its own experts that one of ordinary skill in the art could have readily performed radioimmunoassays (RIA) and compared results of one RIA with another, even where different antibodies, EPO samples, and assay parameters are used. Roche cannot avoid summary judgment by relying on unsubstantiated attorney argument to contradict its own experts, who agree that one of ordinary skill in the art would readily understand the meaning of "units of EPO . . . as determined by radioimmunoassay" and could readily perform an RIA to obtain the recited measurement.

Finally, Roche recasts Amgen's arguments regarding waiver. Rather than addressing the representations it made during *Markman* that each of the terms had a specific construction based on its plain meaning and the intrinsic record, Roche instead sets up a strawman (that Amgen argues that a claim, if construed at *Markman*, cannot be found indefinite), and then rebuts that strawman with a long litany of case citations. But Roche misses Amgen's point, which is directed to the inconsistency of Roche's positions. For example, for the term "human erythropoietin," Roche's proposed claim construction specifically referred to a product "having ***the amino acid sequence of erythropoietin isolated from human urine***" (as produced by certain cells). In support of this construction, Roche represented that its definition was supported by the intrinsic record and was consistent with the understanding of an ordinarily skilled artisan.[10] Now that the term has been construed by the Court to require a product "having the amino acid

[9] Roche Opp. at 1-2.

[10] Roche's 3/5/07 Opening Memorandum in Support of Its Proposed Claim Construction (Docket No. 311) at 6-7.

sequence of human EPO, such as ***the amino acid sequence of EPO isolated from human urine,***"[11] how can Roche argue that the claim is indefinite?

As to the adequacy of Dr. Lin's enablement and written description, Roche's misdirection is even more transparent. Roche dedicates one-quarter of its opposition to issues that Amgen did not raise in its motion and are not relevant to the question actually posed in Amgen's motion: should this Court's enablement and written description inquiry focus on whether Dr. Lin enabled and described the ***claimed inventions***, or should it instead focus on whether he enabled and described elements (like Roche's peg) that are not recited in the claims? Rather than address that question, Roche argues that Amgen is estopped from claiming peg-EPO. Putting aside the fact that Roche's arguments were previously considered and rejected by the Court in its *Markman* ruling, Roche's arguments simply fail to address whether Dr. Lin's specification adequately enabled and described the inventions actually claimed by Dr. Lin.

Contrary to Roche's premise, an inventor need not enable and describe every conceivable embodiment that may use, incorporate or otherwise infringe the claimed invention. The law requires only that Dr. Lin describe and enable the inventions he claimed, not the products that may infringe those claims. Moreover, even accepting Roche's errant logic, peg-EPO is neither an EPO analog nor a synthetic polypeptide, as defined in Dr. Lin's specification. Thus, even if the Court were to assume, for purposes of summary judgment, that Amgen had forfeited its right to assert Dr. Lin's claims against "EPO analogs" and "synthetic polypeptides," that fact would not estop Amgen from asserting Lin's claims against Roche's peg-EPO product, which contains an EPO molecule that has the same amino acid sequence and glycosylation composition as Dr. Lin's claimed EPO.[12]

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[11] 7/3/07 Memorandum and Order (Docket No. 613) at 15.

[12] Roche also argues at length that pegylation techniques were unpredictable in 1983-1984. Docket No. 630 at 18-20. For purposes of summary judgment, Amgen assumes this alleged fact,

Because Roche concedes that there are no material issues of fact, and because it fails to address or rebut the facts set forth in Amgen's motion — instead seeking only to misdirect and obfuscate —Amgen's motion should be granted.

II. ARGUMENT

A. "Non-naturally occurring" is a negative source limitation that has a definite meaning.

Tellingly, Roche's opposition does not challenge that "non-naturally occurring" is a negative source limitation. Nor does it deny that the Federal Circuit has previously stated that such limitation was added "merely [to] prevent[s] Amgen from claiming the human EPO produced in the natural course,"[13] and "mean[s] just what [it] say[s] . . . [it] limit[s] only the source from which the EPO is obtained, . . ."[14]

Rather, Roche's opposition and cross-referenced motion[15] challenges the novelty of Dr. Lin's claimed invention in the guise of an indefiniteness challenge. Because Roche lacks the evidence to prove that any prior art, natural-source EPO glycoprotein is identical to the claimed EPO glycoprotein products made from man-made sources, it resorts to an erroneous legal theory to ignore one claim limitation ("product of the expression of in a mammalian host cell of an exogenous DNA sequence") and contorts the meaning of another limitation ("non-naturally occurring") in an attempt to invalidate Amgen's claims. Roche's misdirection is laid bare by the

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while irrelevant to Amgen's motion, is true. If Roche is allowed to present evidence at trial regarding this issue, Amgen will present evidence and testimony contradicting Roche's arguments.

[13] *Amgen Inc v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) (*Amgen II*); *see* Roche's Opp. at 5.

[14] *Amgen II*, 314 F.3d at 1330 n.5. Contrary to Roche's assertions, the Court's July 3, 2007 Order, repeating the express construction given to "non-naturally occurring," does not challenge or undermine these findings. Rather, it only repeats the construction provided in the *TKT* litigation. *See* Docket No. 613 at 30-32.

[15] Roche also refers to its motion for summary judgment that the asserted '933 claims are invalid (*see* Roche's Opp. at 4, n. 7). Amgen respectfully requests that the Court also refer to Amgen's

question Roche poses in its motion: "[H]ow (if at all) can the product of this claim be distinguished from the urinary erythropoietin prior art cited by the Patent Office?" As Roche surely knows, not only is the question of novelty irrelevant to the definiteness of a limitation under § 112, ¶ 2, but the novelty of a claimed invention is determined by the entirety of claim language, not a single limitation.[16] Roche's argument is nothing more than a naked attempt to lead this Court astray.

At bottom, Roche's argument is built on four assertions: (1) Amgen allegedly relied on the "non-naturally occurring" limitation alone to distinguish its claims over the prior art during prosecution; (2) as a matter of law, "[t]he process limitations set forth in the '933 claims cannot distinguish the claim over the prior art"; (3) the only structural distinctions that Amgen can rely on to distinguish its claimed products over the prior art are distinctions in glycosylation; and (4) the Court has already held that glycosylation differences are indefinite. None of these assertions are grounded in fact or applicable law.

As to Roche's first argument, Roche's reliance on a single snippet from the '933 patent's prosecution history is misleading and inconsistent with established case law. Like the whole of Roche's opposition, Roche's assertion ignores the remainder of the history and the proposed claim language at issue when the cited comment was made. As more fully set forth in Amgen's motion, the term "non-naturally occurring" was added to unasserted '933 claim 1 with the limitation "a glycosylation which differs from that of human urinary erythropoietin." Obviously, the terms cannot mean the same thing.[17] "Non-naturally occurring" was added as a negative

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Opposition to that memorandum (Docket No. 580).

[16] Docket No. 580 at 10-11.

[17] *Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 448 F.3d 1324, 1333 n.3 (Fed. Cir. 2006) ("[T]he use of two terms in a claim requires that they connote different *meanings*. . . ."). *See also Tandon Corp. v. United States Int'l Trade Comm'n,* 831 F.2d 1017, 1023 (Fed. Cir. 1987) (where claims use different terms, those differences are presumed to reflect a difference in the

source limitation — a point Roche seems to acknowledge in the context of its Opposition to Amgen's Motion for Summary Judgment of No Obviousness-Type Double Patenting[18] and one which the examiner expressly recognized in the Record of Examiner Interview which immediately preceded the amendment introducing the "non-naturally occurring" limitation.[19] Finally, the law directs that the novelty requirement of § 102 applies to the claims as a whole, not to individual limitations.[20] Thus, the snippet cited in Roche's motion was directed to the then pending claim, considered as a whole, rather than the limitation "non-naturally occurring" only, as Roche advocates.

Roche's second assertion, discounting the limitation "product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin," as it appears in '933 claim 3, misreads or misconstrues the Federal Circuit's statements in the *TKT* litigation regarding process limitations. The Federal Circuit stated, "a product cannot be rendered patentable ***solely*** by the addition of source or process limitations."[21] As explained in the Court's July 3 Claims Construction Order, however, this does not mean that the process limitation cannot be used to distinguish a claimed product over the prior art if the process results in a structurally distinct product.[22]

And while no more relevant to an indefinite inquiry than Roche's third point, the record

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scope of the claims).

[18] Docket No. 568 at 7 (acknowledging that the term "non-naturally occurring" was added to exclude any "EPO polypeptide [that] could not be isolated from natural sources").

[19] 7/9/07 Toms Decl. (Docket No. 675) at Ex. 1 (at 6).

[20] *See e.g., Hakim v. Cannon Advent Group, PLC*, 479 F.3d 1313, 1319 (Fed. Cir. 2007) (a claim is anticipated when "all of the elements and limitations of the claim are described in a single prior art reference") (citation omitted).

[21] *Amgen II*, 313 F.3d at 1354, n.2 (emphasis added).

[22] Docket No. 613 at 18 *citing In re Luck*, 476 F.2d 650, 653 (C.C.P.A. 1973) and *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006). *See also, Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 320, n. 138 (D. Mass. 2004) (*Amgen III*).

is replete with evidence that EPO glycoproteins of '933 claim 3, and its dependent claims, are structurally distinct from prior art EPOs as a result of at least the post-translational modifications that are made by mammalian cells to the EPO polypeptides they express. As Dr. Goldwasser testified at length at deposition in this matter, experiments reported in a paper published in 1997[23] demonstrate numerous other differences between recombinant and urinary erythropoietin. These differences, including specific activity,[24] accessibility to iodination,[25] inactivation by iodination,[26] trypsin inactivation,[27] and circular dichroism,[28] each indicates that recombinant and urinary erythropoietin differ conformationally (structurally), i.e., in the way the molecules of each are folded.[29] All of these differences, as well as differences in glycosylation, are the direct consequence of the process of production recited in 933 claim 1 and distinguish the claimed invention from prior art naturally-occurring urinary EPO.[30]

As to Roche's final point, the fact that the limitation "glycosylation which differs from

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[23] 6/29/07 Bier Declaration in Support of Amgen's Opposition to Roche's Motion for Summary Judgment regarding the asserted '933 claims (Docket No. 582) at Ex. 2 (2/26/07 Goldwasser Tr. at 468:10-469:8); *id.* at Ex. 3 (C. Kung and E. Goldwasser, "A Probable Conformational Difference Between Recombinant and Urinary Erythropoietins," *Proteins: Structure, Function, and Genetics*, 28(1):94-98 (1997)).

[24] *Id.* at Ex. 2 (2/26/07 Goldwasser Tr. at 461:8-464:6); *see also* Miyake et al., "Purification of Human Erythropoietin," *J. Biol. Chem.*, 252(15):5558-5564 (1977) (Docket No. 502, Ex. E-4) at 5563 (reporting specific activity for urinary EPO of 70,400 unites/mg of protein).

[25] Docket No. 582, Ex. 2 (2/26/07 Goldwasser Tr. at 471:19-473:8).

[26] *Id*. at 474:1-475:13.

[27] *Id.* at 475:15-476:16.

[28] *Id.* at 476:21-478:18.

[29] *Id.* at 463:12-464:6.

[30] Because all of the other asserted '933 claims depend from '933 Claim 3, they are also distinct from the prior art for this reason. Additionally, each of the six asserted dependent claims also contains at least one ***further*** limitation that distinguishes what is claimed from the prior art. Thus, even if Claim 3 were to be found to have been anticipated, Claims 7, 8, 9, 11, 12, and 14 Roche would have to prove that each is invalid separately — without reference to the "non-naturally occurring limitation — by clear and convincing evidence. And that is something Roche, in its various motions for summary judgment, has not even attempted to do.

that of human urinary erythropoietin" was found to be indefinite is not relevant to whether "non-naturally occurring" satisfies the definiteness requirement of § 112. The two different limitations, appearing in the same claim, cannot be construed to mean the same thing.[31] And, in considering '933 Claim 1, the Federal Circuit assigned the term "non-naturally occurring" a definite meaning, and then focused on the term "human urinary erythropoietin" (in the context of defining glycosylation differences), not "non-naturally occurring," to find the claim indefinite.[32]

B. Because "capable upon growth in culture," as it appears in '349 claim 7, refers to the specific culture conditions practiced by an alleged infringer, it is definite.

Roche's opposition does not seriously challenge either the facts or arguments raised in Amgen's motion as to the term "capable upon/of," except to challenge whether a radioimmunoassay can be used to measure for the presence of EPO, and, incredibly, to argue that '349 claim 7 "covers production of 'erythropoetin' without regard to how much is actually being produced, as long as the vertebrate cells will produce, under some set of conditions, the requisite number of 'U of erythropoietin.'"[33]

As set forth below, Roche's challenge to whether a radioimmunoassay can be used to measure for the presence of EPO is makeweight. Roche's position that no production level is required by '349 claim 7 is worse since it is in direct odds with its motion for summary judgment that '349 claim 7 is not infringed.[34] In that motion, Roche argues that Amgen has failed to prove that Roche's CHO cells produced the ***requisite level of EPO*** on the ground that, *inter alia*, Amgen failed to use the ***specific set*** of conditions used in Roche's commercial process. Roche's

[31] *CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co. KG*, 224 F.3d 1308, 1317 (Fed. Cir. 2000) ("In the absence of any evidence to the contrary, we must presume that the use of these different terms in the claims connotes different meanings."); *Applied Med. Res. Corp.*, 448 F.3d at 1333 n.3.

[32] *Amgen II*, 314 F. 3d at 1340-42.

[33] Roche's Opp. at 14.

position is also at odds with its opposition to Amgen's motion for summary judgment of no obviousness type double patenting, in which Roche specifically argues that some baseline level of production is required by the '349 claims:

> "[T]hey [one of ordinary skill in the art] would have recognized that the claim required at least some baseline level of production."[35]

Roche cannot create a material issue of fact or avoid summary judgment merely by taking inconsistent positions between its nine summary judgment motions.

C. Roche has failed to offer any issue of material fact that would preclude a finding that "units of erythropoietin . . . as determined by radioimmunoassay" is not indefinite under 35 U.S.C. § 112.

Roche has reduced to three arguments the bases for its argument that the limitation "U of erythropoietin . . . as determined by radioimmunoassay" is indefinite: (1) RIAs cannot distinguish between EPOs and non-EPOs; (2) "U of erythropoietin" is a measure of biological activity and RIA does not measure activity; and (3) many standards for RIAs were known as of 1983, and each would have resulted in a different result.[36] Roche has offered no evidence to support these arguments, and in fact, they are contradicted by Roche's own documents and experts.

As to Roche's first argument, as more fully set forth in Amgen's Opposition to Roche's motion for summary judgment regarding '349 claim 7,[37] Roche offers absolutely no ***evidence*** in support of its implicit assertion that Roche's cells produce EPO fragments or that RIAs do not distinguish between EPO and EPO fragments. Rather, Roche resorts to mischaracterizing the testimony of Amgen's experts.[38] Moreover, even if there were evidence that Roche's cells

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[34] See Docket No. 539.

[35] See Docket No.568 at 6, n. 4.

[36] Roche Opp. at 12.

[37] Docket No. 628 at 5-7.

[38] *Id.* at 5-6.

produced the "EPO fragments" postulated by Roche, Roche has made ***no*** factual showing regarding the expected effect of such "EPO fragments" on the number of units of EPO determined by radioimmunoassay. Roche's argument consists solely of a ***hypothesis*** that unidentified EPO "fragments" of unspecified origin might react with an anti-EPO antibody in a RIA to produce incorrect results. There is really no question that one can use an RIA to measure the amount of EPO in a biological sample. Roche admitted as much in its proposed stipulation that its process satisfies this limitation of the '349 claims, and in its BLA submission to the FDA.[39]

Roche's second argument, that the limitation is nonsensical because "units" refers to "biological activity" and RIAs do not measure for biological activity, is contradicted by the claim language itself, the intrinsic record, and the prior art, all of which establish that the phrase "U of erythropoietin . . . ***as determined by radioimmunoassay***" would have been understood by one of ordinary skill to mean exactly what it says: that the number of Units of EPO produced by the recited cells in the process of claim 7 is to be determined by an appropriately conducted RIA.[40]

Claim 7 itself says nothing about measuring *in vivo* biological activity of the EPO produced by the recited cells, whether by RIA or any other method. Dr. Lin's patent specification separately and expressly describes three types of assays to assess the EPO produced by Dr. Lin's genetically engineered cells grown in culture: an RIA, an *in vitro* cellular assay, and *in vivo* animal assays.[41] The '349 patent never refers to the determination of *in vivo* biological

[39] *See* 7/5/07 Pendleton Declaration in Support of Amgen's Opposition to Roche's Motion for Summary Judgment as to the '349 claims (Docket No. 634) at Ex. 29; *id.* at Ex. 18 (at, *e.g.*, R005312695, R005312714–16, R005312772–74); *id.* at Ex. 5 (at ¶¶ 36–40).

[40] *See id.* at Ex. 6 (at ¶ 119), 187; *id.* at Ex. 5 (at ¶¶ 30–33).

[41] *See id.* at Ex. 2 ('349 Patent at col. 16:40-17:9 (radioimmunoassay); col. 25:1-15 (*in vitro* and *in vivo* assays)).

activity using an RIA. To the contrary, the '349 specification consistently distinguishes immunological activity as determined by RIA with *in vivo* biological activity as determined by means of an *in vivo* bioassay.[42] One of ordinary skill reading the '349 claim language in light of the specification could not have concluded that the claims required the determination of *in vivo* biological activity by RIA.

Moreover, ***all*** of the prior-art publications discussing EPO RIAs, including publications by Roche's retained experts Drs. Shouval, Fisher, Gaylis, and Zaroulis, uniformly reported the results of EPO RIAs in "Units," "U/ml" (*i.e.*, Units of erythropoietin per milliliter of sample), or similar terms.[43] Indeed, Roche itself reported the results of EPO RIAs in terms of Units ("mU/ml") in its own submissions to the FDA seeking approval for its peg-EPO product.[44]

Roche's third argument is also incorrect. First, it assumes that claim 7 should be construed to require the determination of *in vivo* biological activity by RIA. For the reasons discussed above, this is a false assumption. Second, Roche's factual assumption is incorrect because one of ordinary skill would have obtained the same results in an EPO RIA using any properly calibrated standard.[45] The very nature and purpose of a ***standard*** is to permit

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[42] *See id.* ('349 Patent at col. 13:45–54 (distinguishing "immunological" properties from "*in vivo* and *in vitro* biological activities of EPO"); 14:66-15:12 (same); 25:65-26:5 (discussing "immunological properties" of EPO determined by radioimmunoassay); 27:59–67 (presenting results of radioimmunoassay, *in vitro*, and *in vivo* assays together, all in terms of "U/ml")).

[43] *See id.* at Ex. 10 (Sherwood & Goldwasser (1979)) at, *e.g.*, 891 (Tables 2 & 3)); *id.* at Ex. 24 (Garcia *et al.* (1979) at, *e.g.*, 412 (Table I and accompanying text)); *id.* at Ex. 23 (Zaroulis *et al*. (1981) at, *e.g.*, 89 (Fig. 2; Tables I & II)); *id.* at Ex. 8 (Goldwasser and Sherwood (1981) at, *e.g.*, 359); *id. at* Ex. 28 (Rege *et al*. (1982) at, *e.g.*, 836 (Table IV)); *id.* at Ex. 30 (Koeffler & Goldwasser (1981)) at, *e.g.*, 46 (Table I)); *id.* at Ex. 25 (Cotes *et al*. (1982) at, *e.g.*, 430 (Table I)); *id.* at Ex. 31 (Thomas *et al*. (1983) at, *e.g.*, 798 (Table 3)); *id*. at Ex. 32 (Garcia (1974) at, *e.g.*, 280 (Table I)); *id.* at Ex. 35 (Lertora *et al*. (1975) at, *e.g.*, 146 (Figure 4)); *id.* at Ex. 33 (Goldwasser *et al*. (1975) at, *e.g.*, 322 (Table 6)); and *id.* at Ex. 34 (Lange *et al*. (1980) at 206–207 (Table 1)).

[44] *Id.* at Ex. 18 (at R005312695, R005312714–16, R005312772–74); *id.* at Ex. 5 (at ¶ 36–40).

[45] *See, e.g.*, *id.* at Ex. 22 (at 10-11 (describing calibration of successive international EPO reference standards in terms of the activity of the preceding standard)); *see also id.* at Ex. 6 (at ¶¶

laboratories to compare results over time despite differences in their samples, techniques, and reagents.[46] Given this, it is not surprising that the prior art, and even Roche's own prior art experts, uniformly refute Roche's argument.

For example, Roche's expert regarding RIAs in this case, Dr. Charles Zaroulis, published a scientific article in 1981 describing the use of an RIA to measure EPO concentrations in human serum samples. In that paper, Dr. Zaroulis and his colleagues stated that "[o]ur normal EP concentrations were similar to those reported by Sherwood and Goldwasser [26] and Garcia, Sherwood, and Goldwasser [25]."[47] In the RIAs reported in his paper, Dr. Zaroulis used a standard with a specific activity of 62 U/mg, while Drs. Sherwood and Goldwasser used a standard having a specific activity of 70,400 U/mg,[48] and Drs. Garcia, Sherwood, & Goldwasser used a standard having a specific activity of 5 U/mg.[49] Despite the fact that the three groups used three different EPO preparations as standards, preparations whose specific activities differed by as much as 14,000-fold, Dr. Zaroulis was perfectly comfortable comparing the RIA results found with each of the three standards, reporting that all of the studies found "similar" EPO concentrations in the sera of normal individuals.[50] It is not surprising in view of this record that Roche's own expert, Dr. Shouval, testified at deposition, that one of ordinary skill in the art could have "easily" understood the meaning of the limitation "U of erythropoietin . . . as

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128, 140, 144–50, 168, 177–78, & 183); *id.* at Ex. 5 (at ¶¶ 60, 83, 88, 94, 100).

[46] *See id.* at Ex. 6 (at ¶ 144); *see also id.* at Ex. 4 (at 179:16–20).

[47] *See id.* at Ex. 23 (at 91).

[48] *See id.* at Ex. 10 (at 885 (reporting the specific activity of the pure urinary EPO used as the EPO standard as "70,400 U/mg protein, based on the activity of the [1st] International Reference Preparation")).

[49] *See id.* at Ex. 24 at 409 ("The second International Reference Preparation of human erythropoietin was used as a standard [in the reported RIA analyses].").

[50] *See id.* at Ex. 6 (at ¶¶ 177, 183). *See also id.* at Ex. 25 (at 428–29 (using 1st and 2nd IRPs as EPO standards in RIA and reporting their specific activity as 1 and 5 U/mg of protein, respectively)).

determined by radioimmunoassay."[51]

D. "Human erythropoietin," as construed by the Court, is definite.

According to Roche, the Court's construction of "human erythropoietin" is insolubly ambiguous and renders Dr. Lin's asserted claims invalid. In support of this position, Roche first argues that because Amgen's claims fail to recite a "particular sequence," its claims are indefinite. This first argument is a written description argument masked in definiteness terminology. As set forth more fully in Amgen's Opposition to Roche's first Motion for Summary Judgment of Invalidity of '422 claim 1,[52] as either a written description or indefiniteness challenge, Roche is wrong.

Throughout his specification, Dr. Lin affirmatively states that the products of his invention include "human erythropoietin."[53] To demonstrate this fact, Dr. Lin teaches that he obtains his product using the DNA sequence encoding human erythropoietin,[54] that the N-terminal amino acid sequence of his product corresponds to the N-terminal sequence of human urinary EPO,[55] that his product possesses the expected biological activity of human erythropoietin, as measured using a variety of *in vivo* and *in vitro* assays,[56] and that his product is appropriately glycosylated.[57] Indeed, this is why this Court previously found, and the Federal Circuit affirmed, that '422 claim 1 satisfies § 112's written description requirement.[58]

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[51] Docket No. 534 at Ex. 11 (5/24/07 Shouval Tr. at 194:17-195:11); *id* (at 198:14-199:10 (term "units per ml of cell culture medium," as measured by RIA, is "self explanatory")); *id.* at Ex. 15, 6/8/07 Gaylis Tr. at 273:16-275:12; Ex. 16, 5/17/07 McLawhon Tr. at 24:18-26:18.

[52] *See* Docket No. 565.

[53] *See, e.g.*, Docket No. 534 at Ex. 3 ('933 Patent, at col. 27:47-51).

[54] *Id.* (at Examples 7, 10, and 11).

[55] *Id.* (at col. 28:11-12).

[56] *Id.* (at col. 28:1-28).

[57] *See, generally, id.* (at col. 28:33-29:7).

[58] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 151 (D. Mass. 2001) (*Amgen*

Moreover, there is no dispute that the product produced by following the process exemplified in Dr. Lin's preferred embodiment, 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.[59] As such, even if Amgen's claim is limited to a "particular sequence" and that sequence is the 1-165 amino acid sequence of Dr. Goldwasser's uEPO, as Roche asserts in its opposition, Dr. Lin's specification plainly satisfies § 112's written description requirement.[60]

Roche's second argument, based on so-called "errors" in Dr. Lin's specification, is no more compelling. For example, regarding the fragments described in Example 1 of Dr. Lin's specification, as expressly set forth in the specification, and as one of ordinary skill in 1983 would have understood, microsequencing of peptides was far from an exact or error-free process. Thus, as Dr. Lin noted in his specification in discussing the discrepancies in the urinary EPO peptide sequences disclosed in Example 1 and the deduced EPO sequence shown at Figure 6, his

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I), *aff'd* 314 F.3d 1313 (Fed. Cir. 2003).

[59] 6/29/07 Sasaki-Baxley Declaration in Support of Amgen's Opposition to Roche's Motion for Summary Judgment that '422 claim 1 is Invalid (Docket No. 567) at Ex. A (3/28/07 Lin Depo. Tr.) at 223:16-20); Roche's 6/11/007 Memorandum in Support of its Motion for Summary Judgment That '422 Claim 1 is Invalid (Docket No .483) at Exh. 5 (Recny *et al. J. Biol. Chem.*, 262(35): 17156-163 (1987)).

[60] *Regents of the Univ. of New Mexico v. Knight*, 321 F.3d 1111, 1122 (Fed. Cir. 2003); *Kennecott Corp. v. Kyocera*, 835 F.2d 1419, 1421-23 (Fed. Cir. 1987). In its reply in support of its motion for summary judgment that '422 claim 1 is invalid, Roche discounts the applicability of the *Regents* and *Kennecott* cases in favor of *Hyatt v. Boone*, 146 F.3d 1348, 1354-55 (Fed. Cir. 1998) and *In re Wallach*, 378 F.3d 1330, 1334-35 (Fed. Cir, 2004). *See* Docket No. 678 at 5-9. Both *Hyatt* and *Wallach* are inapposite. As evidenced by Roche's opposition, as well as its multiple motions for summary judgment, Roche wants this Court to read a specific sequence limitation (*e.g.*, the "mature amino acid sequence of Fig. 6" limitation in the unasserted '080 claims) into the claim, ostensibly to avoid infringement. Roche then asks the specification to demonstrate possession of this imported limitation (or the construction of the limitation) rather than the claimed invention, which is not what the statute of the case law requires. Roche asserts that *Hyatt* and *Wallach* are applicable. But, '422 claim 1 is not directed to a "pharmaceutical composition comprising human erythropoietin having the mature amino acid sequence of Figure 6" and thus Roche's reliance on *Hyatt* and *Wallach* is misplaced.

claims were not limited to human erythropoietins having the deduced Figure 6 sequence. Rather they would include allelic variants of human erythropoietin:

> It is worthy of note that the specific amino acid sequence of FIG. 6 likely constitutes that of a naturally occurring allelic form of human erythropoietin. Support for this position is found in the results of continued efforts at sequencing of urinary isolates of human erythropoietin which provided the finding that a significant number of erythropoietin molecules therin [sic] have a methionine at residue 126 as opposed to a serine as shown in the Figure.[61]

Roche's assertions to the contrary are not supported by the intrinsic record and the extrinsic evidence cited in its brief does not contradict this definition. Likewise, Roche's speculation that allelic variants of human erythropoietin are common place and "might" fall in the millions, is notably unsupported by any citation to the published literature.

Finally, Roche's arguments that it did not waive its right to challenge Dr. Lin's claims miss the point. The point is that Roche offered a similar construction of "human erythropoietin" at *Markman* as the Court has adopted. The only difference is 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:[62]

> 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.[63]

At *Markman*, Roche argued that its proffered definition "is supported by the patentee's definition and use of this term in the specification and the prosecution histories,"[64] and was

[61] Docket No. 534 at Ex. 3 ('933 Patent, at col. 21:11-19); *see also, id.* (at col. 35:17-39).

[62] In taking this position, Roche sought to read the term "purified from mammalian cells grown in culture" out of the claim all together, asserting that it was a "source limitation which does not define the claimed product. Docket No. 311 at 2.

[63] *Id.* at 1.

[64] *Id.* at 6.

consistent with the understanding of an ordinarily skilled artisan.[65] Having failed to persuade the Court to adopt its attempt to read additional limitations into the term "human erythropoietin," Roche now asserts that the term is unintelligible and without meaning to one of ordinary skill in the art. It should not be allowed to do so. Either Dr. Lin's specification and the intrinsic record were sufficient to define "human erythropoietin" by reference to the amino acid sequence of human urinary EPO, as Roche previously claimed, or it does not, as Roche now inconsistently asserts.

E. Dr. Lin's specification describes and enables his claimed invention.

Roche does not challenge anywhere in its opposition that Dr. Lin's specification describes and enables how to make a glycosylated human EPO. Rather, by way of its argument that Amgen is estopped from claiming EPO analogs and synthetic EPOs, Roche first challenges whether Amgen may assert Lin's claims against peg-EPO. But that, of course, is a question for claim construction and infringement, not proof of non-enablement or inadequate written description. On the same false premise that an inventor must enable or describe inventions he did not claim, Roche also challenges whether one of ordinary skill in the art could have made peg-EPO in 1983 based on the purported unpredictability in the pegylation arts at that time. Neither argument is relevant to Amgen's motion and thus, even assuming that they are true, Amgen should still prevail.

Putting aside the fact that Roche's estoppel arguments were previously considered and rejected by the Court in its *Markman* ruling, Roche's arguments simply fail to address whether Dr. Lin's specification adequately enabled and described the inventions actually claimed by Dr. Lin. Contrary to Roche's premise, an inventor need not enable and describe every conceivable embodiment that may use, incorporate or otherwise infringe the claimed invention. The law

[65] *Id.* at 6-7.

requires only that Dr. Lin describe and enable the inventions he claimed, not the products that may infringe those claims. Moreover, even accepting Roche's errant logic, peg-EPO is neither an EPO analog nor a synthetic polypeptide, as defined in Dr. Lin's specification. Thus, even if the Court were to assume, for purposes of summary judgment, that Amgen had forfeited its right to assert Dr. Lin's claims against "EPO analogs" and "synthetic polypeptides," that fact would not estop Amgen from asserting Lin's claims against Roche's peg-EPO product, which contains an EPO molecule that has the same amino acid sequence and glycosylation composition as Dr. Lin's claimed EPO. Roche's assertions regarding the state of the "pegylation arts" in 1983 similarly do not preclude summary judgment. Roche does not dispute that Dr. Lin's patents claim, describe, and enable human erythropoietin, EPO glycoprotein products and methods for making the same. Roche's peg-EPO product infringes because it contains the claimed human erythropoietin or glycoprotein products. The presence of additional elements in Roche's accused product, elements, such as peg, ***that are not recited in the claims***, does not negate infringement.[66] Under § 112, however, the proper inquiry is directed to the ***claimed inventions***, not the accused product. Dr. Lin was not required to describe or enable elements such as PEG that are not claimed as his invention.[67]

Roche's attempt to create a requirement that Dr. Lin had to describe and enable additional unclaimed elements ignores the fact that the legal test for both written description and

[66] *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1482 (Fed. Cir. 1984) ("[m]odification by mere *addition* of elements of functions, whenever made, cannot negate infringement without disregard of the long-established [] hornbook law . . . ."); Docket No. 613 at 14 ("this Court does not think it ought to alter the open construction of the term 'human erythropoietin' found in the patent").

[67] However, if the Court rejects Amgen's claim interpretation argument, Amgen does not suggest that the claims are invalid. Amgen has submitted expert testimony addressing Roche's interpretation and establishing that the claims are valid.

enablement focuses only upon the claimed invention, not the accused product.[68] Thus, even taking for purposes of summary judgment Roche's allegations regarding the state of pegylation technology in 1983 as true,[69] because Roche's argument is premised purely upon an incorrect interpretation of the law of written description and enablement, Amgen is entitled to summary judgment of validity on this issue.

III. CONCLUSION

For the reasons set forth above, Amgen respectfully requests that find that Dr. Lin's asserted claims are definite, adequately described, and enabled.

[68] *See Amgen/HMR II*, 314 F.3d at 1333 ("[U]nder our precedent the patentee need only describe the invention *as claimed*, and need not describe an unclaimed method of making the claimed product.") (emphasis added); *Christianson v. Colt Indus. Operating Corp.*, 822 F.2d 1544, 1562 (Fed. Cir. 1987), *vacated on other grounds*, 486 U.S 800 (1988) ("The 'invention' referred to in the enablement requirement of section 112 is the *claimed* invention."); *Wesley Jessen Corp. v. Bausch & Lomb, Inc*., 209 F. Supp. 2d 348, 398 (D. Del. 2002) ("The patent only must enable what is claimed.").

[69] If this Court requires that Amgen rebut at trial Roche's contentions regarding the state of the art in 1983, as it pertains to pegylation techniques and knowledge, Amgen's experts, Drs. Vladamir Torchilin and Nadini Katre are prepared to do so.

Respectfully Submitted,

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