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

MEMORANDUM OF LAW IN SUPPORT OF ROCHE'S 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

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Defendants F. Hoffmann-La Roche Ltd, Roche Diagnostics GmbH, and Hoffmann-La Roche, Inc. (collectively "Roche") submit this memorandum of law in support of their motion for summary judgment that claim 7 of U.S. Patent No. 5,756,349 (the " '349 patent") – the only claim of that patent asserted in this case by Amgen – is invalid, under 35 U.S.C. § 112, on the grounds of indefiniteness, lack of written description, and lack of enablement, and additionally is not infringed.

I. PRELIMINARY STATEMENT

Claim 7 of the '349 patent recites a process for producing erythropoietin using "vertebrate cells" described in claims 1-6 of the patent. The claims characterize those cells as being "capable of" producing a specified number of Units ("U") of erythropoietin ("EPO"), *i.e.*, 100, 500 or 1000, per 10^6 cells in 48 hours as determined by radioimmunoassay ("RIA"). This limitation, present literally or by dependency in all claims of the '349 patent, suffers from three fatal flaws that render claim 7 invalid under 35 U.S.C. § 112 for indefiniteness, inadequate written description, and lack of enablement:

First, RIA is predicated on immunoreactivity, *i.e.*, that anti-EPO antibodies bind to epitopes, which are discrete regions of the molecule. In practice, these antibodies can bind anything that reacts with the antibody including EPO, EPO fragments that include the epitopes, and other cross-reacting molecules. Because RIA does not distinguish EPO from these non-EPO molecules, RIA cannot provide a determination of the amount of "erythropoietin" – as defined by the Court – produced by vertebrate cells of claims 1-6;

Second, RIA does not quantify "U of erythropoietin." Units of EPO are a measure of biological activity. RIA measures antibody binding, including binding of inactive molecules, not biological activity. Thus, the test specified by claims 1-6 cannot determine whether the claimed vertebrate cells produce the requisite number of "U of erythropoietin."

Third, RIA requires the use of reference standards that serve as a basis for calculating the number of EPO molecules present in a test sample and for then converting that result to Units of biological activity based on certain assumptions. RIA results will differ depending on the standard used. Moreover, at the time of the invention of the '349 patent, a number of different standards were being used in performing RIAs. Yet, the claims and specification of the '349 patent fail to identify a standard to use in calculating the "U of erythropoietin . . . as determined by radioimmunoassay."

In addition, claim 7 of the '349 patent is indefinite because vertebrate cells infringe claims 1-6 if they merely are "capable upon growth in culture" of achieving certain EPO Units, regardless of how the cells are actually being used. Indeed, the EPO production capability of cells varies depending on the growth conditions. Consequently, using cells to produce EPO at levels below those of the claims will nonetheless be infringing if under some other growth conditions the very same cells can achieve the specified production levels. Thus, the claims are indefinite for failing to define the boundaries of vertebrate cells that meet the recited limitations.

In short, the specification and the claims of the '349 patent fail to provide critical pieces of information that would permit one of skill in the art to determine whether particular vertebrate cells satisfy the limitations of claims 1-6, and whether use of those cells would infringe claim 7. Therefore, claim 7 is indefinite, lacks written description support in the specification, and is not enabled.

Even if claim 7 of the '349 patent is held not invalid, Amgen cannot meet its burden of proving infringement. Amgen cannot show – as it must to prove infringement of the '349 patent – that Roche uses cells capable of producing the specified number of "U of erythropoietin . . . as determined by radioimmunoassay." In that RIA is based on immunoreactivity and does

not directly measure biological activity, the specified production levels of the claims expressed in "U of erythropoietin . . . as determined by radioimmunoassay" are meaningless. This fundamental flaw in Amgen's claim is exacerbated by the fact that the '349 specification and claims provide no standard through which any RIA measurement can be correlated to biological activity. Amgen's only purported "evidence" of infringement is derived from an experiment that Amgen's own expert, Dr. Kolodner, admits does not meet the claim requirement for "suitable nutrient conditions" as that limitation is explained by Amgen's expert, Dr. Lodish. Moreover, even if Dr. Kolodner had properly conducted his tests, Amgen has not established that Dr. Kolodner measured "erythropoietin" as defined by this Court. In short, Amgen's proffered "evidence" only underscores the indefiniteness of the claims, and confirms Amgen's inability to prove, per the claims of the '349 patent, that Roche uses cells that are capable of producing 100, 500 or 1000 U of erythropoietin per 10^6 cells in 48 hours "as determined by radioimmunoassay.

II. STATEMENT OF FACTS[1]

A. The Asserted Claim

Amgen alleges that Roche infringes one claim of the '349 patent – claim 7. (Ex. A at 3).[2] That claim states: "A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6." (Ex. B at col. 38, ll. 34-36).

Independent Claims 1 and 4, upon which claims 2, 3, 5, 6 and 7 depend, read as follows:[3]

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[1] Roche makes this motion based on certain undisputed facts without waiving its right to assert additional facts, which may be in dispute, should the motion be denied.

[2] All citations to lettered exhibits herein refer to exhibits to the Declaration of Howard S. Suh In Support Of Roche's Motion For Summary Judgment That Claim 7 Of U.S. Patent No. 5,756,349 Is Invalid Under 35 U.S.C. § 112 And Is Not Infringed.

[3] Dependent Claims 2 and 3 depend from 1 and incorporate all limitations of claim 1, but specify 500 U and 1000 U, respectively. Dependent claims 5 and 6 similarly depend from claim 4.

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.
>
> 4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by sradioimmunoassay.

(*Id.* at col. 38, ll. 8-36).[4] Thus, all of the claims of the '349 patent – including asserted claim 7 – require that vertebrate cells be "capable of" of producing 100, 500 or 100 "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay." The term "U of erythropoietin" is not defined in the patent.

B. Erythropoietin

Adopting Amgen's construction, this Court has decided that "human erythropoietin," in the context of the claims of the patents-in-suit, means "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." (Ex. C at 27:8-10, 39:7-10). Amgen does not propose an alternate meaning for the term erythropoietin according to the '349 patent claims. Erythropoietin measurements are often reported in Units ("U") which quantify the biological activity of a sample as measured in an *in vivo* bioassay. (Ex. D at 73:8-74:13; Ex. E at 50:20-52:18, 56:1-6; Ex. F at ¶ 34; Ex. G at ¶ 120).

[4] Amgen alleges that Roche infringes claim 7 by using cells according to claims 1, 2 and 3 of the patent. (Ex. A at 21). Roche alleges that claims 4-6, although not directly asserted by Amgen as a basis for infringement, are likewise invalid. *See infra*, section IV.A.

C. Radioimmunoassay ("RIA")

RIA is a competition binding assay, meaning that it is designed to measure the amount of a protein (such as EPO) in a test sample by quantifying the extent to which the protein in the test sample competes for binding to antibodies that recognize specific portions of the protein with a known amount of radiolabeled protein that can be identified and measured. (Ex. H at ¶ 12). By comparing the assay results with a standard curve generated by testing a series of samples having known concentrations of the protein against the same radiolabeled protein, using various assumptions which may or may not be correct, one can assess how much of the assumed protein was in the unknown sample. (*Id*.) RIA cannot directly determine Units of biological activity of a test sample. (Ex. E at 56:7-10; Ex. I at 64:22-65:25; Ex. F at ¶ 51).

III. LEGAL STANDARD

A. The Summary Judgment Standard

Pursuant to Fed. R. Civ. P. 56(c), summary judgment "shall be rendered forthwith if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." As this Court has stated, "if there are no genuine issues of material fact, summary judgment is appropriate in a patent infringement case as in any other." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 93 (D. Mass. 2001) ("Amgen I").

B. The Definiteness Requirement of 35 U.S.C. § 112

Paragraph 2 of 35 U.S.C. § 112 provides that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." According to the Federal Circuit, the "requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are 'sufficiently precise to permit

a potential competitor to determine whether or not he is infringing.'" *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003) ("Amgen II") (*quoting Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993)).

As this Court stated in *Amgen I*, "[d]etermining whether a claim is definite requires an analysis of 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification.'" *Amgen I* at 156 (quoting *Personalized Media Communications, LLC v. Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998)). "The focus of the inquiry . . . is on the clarity of the claim terms and the extent to which such terms, viewed from the perspective of one of ordinary skill in the art, sufficiently identify the actual invention." *Amgen I* at 156. This notice defines the boundary at which infringement begins so that others can freely experiment and invent outside of those bounds. *Athletic Alternatives, Inc. v. Prince Manufacturing, Inc.*, 73 F.3d 1573, 1581 (Fed. Cir. 1996). Indefiniteness is a question of law to be determined by the court. *Personalized Media Communications*, 161 F.3d at 702.

C. The Written Description Requirement of 35 U.S.C. § 112

35 U.S.C. § 112 ¶ 1 requires that each claim be supported by a "written description of the invention." In order to satisfy the requirements of § 112 ¶ 1, "the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). "[I]t is in the patent specification where the written description requirement must be met." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) (affirming summary judgment on written description grounds).

D. The Enablement Requirement of 35 U.S.C. § 112

35 U.S.C. § 112 ¶ 1 further requires that the specification enable one of skill in the art to make and use the claimed invention. The test for enablement is whether one reasonably skilled in the art could make or use the invention based on the written disclosures of the patent coupled

with information known in the art, without undue experimentation. *Enzo Biochem Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). "In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). The Federal Circuit has found that claims lacked enablement when the patent's specification taught only how to approximate the claimed result. Donald S. Chisum, (2007) Chisum on Patents, Vol. 3, § 7.03(4)(b); *see Nat'l Recovery Techs., Inc. v. Magnetic Separations Sys., Inc.*, 166 F.3d 1190, 1996-98 (Fed. Cir. 1999) (holding that although the patent specification disclosed a method for detecting signals this method was insufficient to select signals as claimed).

E. Noninfringement

"To support a summary judgment of noninfringement it must be shown that, on the correct claim construction, no reasonable jury could have found infringement on the undisputed facts or when all reasonable factual inferences are drawn in favor of the patentee." *Techsearch, LLC v. Intel Corp.*, 286 F.3d 1360, 1371 (Fed. Cir. 2002). Summary judgment of noninfringement is appropriate where the evidence is insufficient to meet an essential part of the legal standard for infringement, because such failure will render all other facts immaterial. *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1537 (Fed. Cir. 1991).

IV. ARGUMENT

A. Claim 7 of the '349 Patent Is Rendered Invalid, Under 35 U.S.C. § 112, By the Production Requirements of 100, 500 or 1000 "U of Erythropoietin . . . as Determined by Radioimmunoassay"

1. RIA Measures More Than "Erythropoietin"

Claim 7 recites a process for producing "erythropoietin" using vertebrate cells having the capability of producing a specified number of "U of erythropoietin . . . as determined by

radioimmunoassay." However, the claims are indefinite and lack written description and enablement because RIA equally measures "erythropoietin" and other materials like EPO fragments that bind to anti-EPO antibodies. RIA, therefore, cannot determine whether the vertebrate cells of the '349 claims can produce "erythropoietin" sufficient to make the process of claim 7 infringing. For the same reason, the patent does not demonstrate that the inventor was in possession of the claimed invention.

This Court has construed "human erythropoietin" to mean "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." (Ex. C at 27:8-10, 39:7-10). Claim 7 therefore covers the use of cells that produce specified levels of a protein having this amino acid sequence.[5]

Because RIA measures how much material in a sample binds to an antibody, and does not measure EPO directly, RIA cannot distinguish between erythropoietin and anything else that will bind to the antibody. Antibodies recognize discrete structural sites on a protein, referred to as "epitopes." Because epitopes are smaller than the entire protein, RIA cannot determine the size of an EPO-like molecule in the sample. (Ex. AA at 280:12-15). Antibodies will therefore recognize other molecules including protein fragments that contain the epitope. (*See* Ex. J at 151:18-152:8).

Amgen's experts concede that RIA detects non-EPO molecules. For example, Dr. McLawhon testified that RIA does not necessarily detect "erythropoietin" in its entirety, and in fact, could recognize "relevant portions" of EPO – in other words, EPO fragments. (Ex. J at 220:4-221:9). One of skill would be left to ***assume*** that a measurement of immunoreactivity

[5] During prosecution of the '933 patent, Amgen tried unsuccessfully to obtain claims to erythropoietin glycoproteins produced by cells transfected with DNA encoding "the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof."

correlated with the biological activity characteristic of full-length EPO. (*Id.*). Amgen expert Dr. Eugene Goldwasser made similar concessions:

> Q. Okay. So let's take that example of what you did in the late '70s, early '80s on the RIA for Epo. When you were doing those experiments, how could you distinguish between the antibody binding to a complete Epo molecule versus a fragment or a smaller than complete Epo molecule?
>
> A. Well, if we were -- if we had a question about it, we would have to do the sorting. ***We couldn't tell by just the RIA itself.***

(Ex. E at 49-50 (emphasis added)).

Dr. Goldwasser confirmed that the presence of fragments can result in overestimating "erythropoietin" levels:

> We have found that several sera from patients with anaemia accompanying chronic renal disease had the expected low titres when assayed in mice but that the titres by RIA were considerably higher than those by bioassay. Preliminary experiments indicate that this discrepancy is probably due to the presence of ***immunologically reactive fragments of erythropoietin*** appreciably smaller than the native hormone. These small fragments can be separated by gel permeation chromatography, and assays for biological activity of this fraction are being done; we predict that the small fragments will be devoid of activity by bioassay, thus accounting for the discrepancy. ***This finding must alert us to the probability that titre by RIA may not always be directly related to the concentration of biologically active erythropoietin.***

(Ex. K (internal citations omitted; emphasis added); *see also* Ex. L).

The '349 patent acknowledges that antibodies useful in an EPO RIA will detect non-EPO molecules. Specifically the patent references an antibody described in an Amgen patent application (issued as U.S. Patent No. 4,558,006). That antibody is disclosed as being "a highly specific monoclonal anti-erythropoietin antibody which is also specifically immunoreactive with a polypeptide comprising . . . the first twenty amino acid residues of mature human erythropoietin. (Ex. B at col. 8, ll. 48-55). Similarly, the '349 patent describes "monoclonal or polyclonal antibodies" which are immunoreactive with both naturally occurring EPO and

"synthetic polypeptides wholly or partially duplicative of continuous sequences of erythropoietin amino acid residues." (*Id.* at col. 10, ll. 48-62). Any of these antibodies if used in an RIA would falsely measure non-EPO molecules such as fragments and other cross-reactive impurities as being "erythropoietin."

In short, even though RIA employs "EPO-specific" antibodies, the assay will actually measure anything that binds to the antibodies. The RIA measures – without distinguishing – 165-amino acid "erythropoietin" as well as certain EPO fragments or other substances. Hence, an RIA will not tell a potential infringer whether it possesses vertebrate cells that produce the number of "U of erythropoietin" recited in the claims. Moreover, the patent does not show that the inventor was in possession of such cells, nor does it teach one of skill in the art how to practice what is claimed.

2. RIA Does Not Measure Biological Activity

RIA measurements are based on immunoreactivity, meaning the binding of the contents of a test sample to antibodies. Amgen's fact witnesses and experts concede, though, that RIA cannot measure biological activity. The fact that material in a test sample binds to anti-EPO antibodies does not prove whether or how biologically active that material is. According to Amgen's Dr. Goldwasser:

> "An RIA is used to measure erythropoietin in a sample based on its immunological reactivity with an antibody raised against EPO. An RIA to measure EPO cannot distinguish between, for instance, unmodified erythropoietin and erythropoietin that has been desialated and has no in vivo biological activity. . . ."

(Ex. G at ¶ 48; *see* Ex. AA at 281: 3-5, 8-10). A 1987 Amgen validation report regarding RIA for EPO similarly states that the "RIA activity is a quantitative measure of native protein structure but not a direct measure of its in vivo potency." (Ex. M at AM ITC 00156691).

RIA merely provides a measure of the amount of EPO (and any immunoreactive fragments, analogs, or even unrelated substances) in the test sample, not Units, a measure of EPO biological activity. Indeed, according to Dr. McLawhon, the RIA "says nothing about the biological activity directly." (Ex. J at 133:24-25). Yet, the claim requires measurement of EPO Units, which since before the time of the invention has been universally understood to be a measure of biological activity. (Ex. E at 50:20-51:21, 52:7-16, 52:20-54:1, 56:1-6; Ex. F at ¶ 75).

Claim 7 of the '349 patent is, therefore, meaningless in that it hinges on "U of erythropoietin" as measured by RIA. RIA alone says nothing about the biological activity of the test sample – *i.e.*, the actual Units present. As such, the RIA cannot prove whether a vertebrate cell has the capability of producing the "U of erythropoietin" required by the claims. Accordingly, the claims are indefinite, the specification lacks written description support for the EPO activity levels of the claims and the patent does not enable the use of cells having the requisite activity.

3. The EPO Production Levels of the Claims Are a Moving Target

Claim 7 of the '349 patent also is indefinite and lacks written description and enablement because the patent prescribes no standard to be used as the basis for comparison in the RIA. To the extent that any information concerning "U of erythropoietin" can be gleaned by RIA, the standard is critical to extracting such information. The '349 claims and specification provide no guidance regarding the appropriate standard to employ and in fact, at the time of the patent application, EPO standards varied. Thus, one of skill in the art would not have known what standard to use to determine the scope of the claim.

Converting the measured amount of protein to "U of erythropoietin" requires reference to a standard. (Ex. H at ¶ 32). Different standards possessing different <u>amounts</u> of EPO by weight

and a different activity of EPO measured in Units will necessarily yield different reported results in an RIA because each has its own distinct conversion factor.

At the time of the invention, though, there were a variety of EPO standards that could be used in RIA testing, each of which would produce a different result. As Amgen consultant and expert Eugene Goldwasser testified: "There never was a single standard." (Ex. E at 53:5). Indeed, during its EPO project, Amgen used different EPO standards for its assays. (Ex. I at 45:18-25, 134:9-11; 170:17-171:20; 184:14-185:2). Importantly, however, the '349 patent does not specify what standard is to be used in the RIA recited in the claims. (Ex. B at col. 16, line 43; Ex. J at 131:10-16).

The appendix to a November 2, 1990 memo by George Rathmann, then CEO of Amgen, reflects the muddled history of the EPO standard. The first international reference standard, "IRP #1," was adopted in the 1960's. (Ex. O at AM-ITC 00558662). A second standard, "IRP #2," was established by the National Institute for Biological Standards and Control (NIBSAC) in 1972 even though "the data which determined the standard clearly showed strong heterogeneity among the various laboratories and assay methodologies." (*Id.*; *see* Ex. P). IRP #2 demonstrated "wide variability from laboratory to laboratory and methodology to methodology." (Ex. O at AM-ITC 00558662). In connection with development of another standard to replace IRP #2, Dr. Goldwasser told NIBSAC that "[t]his immense effort on your part and by all the collaborating labs revealed that the second IRP is a rotten standard." (Ex. Q at UCH000005950-51 (emphasis added); *see* Ex. N at 177:21-178:7). Amgen ultimately deemed IRP #2 "not a suitable standard." (Ex. O at AM-ITC 00558660).

Rather than rely on IRP #2 as a standard for its assays, Amgen turned to various other standards. Amgen calibrated its recombinant EPO against CAT-1, prepared by Dr. Goldwasser,

which was a partially purified EPO from the pooled urine of a number of aplastic anemia patients. (Ex. I at 54:13-57:10). According to Amgen scientist Dr. Joan Egrie, Amgen used CAT-1, rather than the international standard, in performing the work described in the '349 patent. (*Id.* at 134:9-137:23; 194:7-16). CAT-1 ***was not calibrated*** against IRP #2. (Ex. Z at AM-ITC 00550542). When the supply of CAT-1 was exhausted, Amgen began using another standard,"Lot 82," which was an EPO obtained from its business partner Kirin that was purified from the urine of a single patient. (Ex. I at 60-61; Ex. R at AM-ITC 00134725). However, Lot 82 was also "in limited supply." (Ex. S at AM-ITC 00061675; Ex. I at 45-46, 52). Amgen also developed and used a "Mutual EPO Standard" with Kirin, which, in 1985, Kirin suggested they should send to the WHO to become ***IRP #3***. (Ex. Z at AM-ITC 00550541-44; Ex. CC at AM-ITC 00550778; Ex. DD at AM-ITC 00550986).

Amgen's own experience with different standards for its assays demonstrates the absolute necessity of specifically identifying the standard used in an assay, because this was the only clear link back to Units of EPO. George Rathmann confirmed that "if one expressed international units in the time period of 1985-87, it might be assumed that the reference standard was IRP #2, but unless the precise method to be used was defined, there would be no basis for stating international units." (Ex. O at AM-ITC 00558660). In a March 15, 1990 memo Rathmann wrote the following about the measurement of EPO activity:

> I think we should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units ***until we can establish an excellent correlation with international units*** . . . . I think we should understand how any standard can deviate from 'parallelism' trying to relate to international units.

(Ex. T at AM-ITC 00558619). Amgen thus confirmed that years after the patent's filing, EPO standards were still poorly characterized and varied.

Amgen has long maintained that the results of an RIA analysis of an unknown sample containing EPO will depend on the standard that is used in the assay. Yet, the standard to be used in an RIA has never been well settled and neither the specification nor the claims of the '349 patent identify a standard to be used. Consequently, the requirements that the cells of the '349 patent be able to produce 100, 500 or 1000 "U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay" is a meaningless limitation that constitutes an indefinite standard by which to measure the capabilities of EPO producing cells. Moreover, the patent specification does not teach one of skill in the art to make or use the invention as claimed in the '349 patent because the specific standard to use in determining "U of erythropoietin" produced by vertebrate cells is not disclosed.

Unknown test samples have, by definition, an undetermined amount of EPO and an undetermined number of Units of biological activity. In the unknown, the RIA measures amount by comparison to the standard and reports Units of EPO as if the unknown had the same specific activity as the standard. The RIA disclosed in the patent, therefore, requires one to assume – without basis – that the specific activity of the unknown test sample equals that of the standard test sample.

In short, claims 1-6 are hopelessly indefinite for failing to disclose a particular standard to use in the RIA specified by the claim. The indefiniteness would be exacerbated if, as Amgen asserts, prior art urinary EPO, from which all standards would have been derived, are structurally distinct in a material way from recombinant EPO.

4. Claim 7 of the '349 Patent Is Invalid for Reciting the Limitation "Capable Of"

Claim 7 of the '349 patent claims a process for reducing EPO by "culturing, under suitable nutrient conditions, vertebrate cells" which are "capable of" achieving the EPO

production levels set forth in claims 1-6 (which are discussed above) "in 48 hours." The "suitable nutrient conditions" are not recited. Claim 7 thus covers production of "erythropoietin" without regard to how much is actually being produced, as long as the vertebrate cells employed will produce, under some set of conditions, the "U of erythropoietin" recited in claims 1-6.

One of Roche's experts, Dr. Thomas Kadesch, a biochemist in the Department of Genetics at the University of Pennsylvania, explains in his expert report that "[t]here are infinite number of nutrient conditions that one could employ to grow vertebrate cells in culture that would effect the production level of protein." (Ex. U at ¶ 46). Dr. Kadesch points out that "[a] person of skill in the art could run [tests under] hundreds of conditions and never be certain" of being outside the claims of the '349 patent which "only require cells that are capable of achieving certain production levels." (*Id.* at ¶ 48). A potential infringer producing EPO at a level below that specified in the claims, therefore, cannot determine whether the cells being used would nonetheless satisfy the claims because, under other conditions, they may achieve the specified production levels. (*See also* Ex. V at ¶ 50). New cell culture techniques and growth media conditions are constantly being developed. Therefore, non-infringing vertebrate cells that ***today*** cannot produce the levels of EPO required by the claims, even if cultured under suitable nutrient conditions, may ***tomorrow***, under new culture conditions, be shown to be infringing.

Hence, it is impossible for a potential infringer to determine whether cells being used to produce EPO, at whatever level, are, in fact, cells which, under some set of conditions, are "capable of" producing EPO at the levels recited in the claims of the '349 patent. Consequently, the "capable of" limitation renders claim 7 of the '349 patent indefinite. *See Honeywell Int'l, Inc v. Int'l Trade Comm'n*, 341 F.3d 1332, 1341 (Fed. Cir. 2003) ("Because the sample preparation

method is critical in determining [the melting point elevation]. . . . [w]ithout knowing which sample preparation method to use one cannot discern whether a yarn was produced using the claimed process [which required that the yarn have a specified melting point elevation at a given point during the production process]. . . . [T]he testing results will necessarily fall within or outside the claim scope depending on the sample preparation method chosen."); *Morton Int'l, Inc. v. Cardinal Chemical Co.*, 5 F.3d at 1470 (Fed. Cir. 1993) (affirming indefiniteness holding where district court "found that the claimed compounds cannot be identified by testing and that one skilled in the art could not determine whether a given compound was within the scope of the claims"). Moreover, given the vagueness of the "capable of" limitation, the patent would not make clear to one of skill in the art that the inventor was in possession of the claimed invention and would not teach how to practice the invention.

Significantly, during prosecution of patent application no. 07/113,179, parent to the '349 patent, the examiner (then Robert Hodges) rejected a claim to a process for preparing a biologically active glycosylated polypeptide which process included "growing a mammalian host cell which is *capable of* effecting post-translational glycosylation of polypeptides expressed therein." (Ex. W at AM-ITC 00953207 (emphasis added)). In a September 1, 1993 office action Examiner Hodges deemed the claim "vague and indefinite in the recitation of 'a host cell capable of effecting post-translational glycosylation of polypeptides.'" Mr. Hodges explained:

> "It is not clear what relationship applicant intends between the glycosylation of polypeptides and the recited cell. A cell capable of effecting post-translational glycosylation of polypeptides is not necessarily effecting post-translation and so it is not clear if applicants intend to claim said a cell which is in fact effecting post-translational glycosylation, said cell which is not effecting post-translational glycosylation, or both. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison,* 69 USPQ 138."

(Ex. X at AM-ITC 00953598). Claim 65 was then cancelled by the applicant. (Ex. Y at AM-ITC 00953638).

The claims of the continuation application which resulted in the issuance of the '349 patent, nonetheless claimed cells "capable of producing" specified levels of EPO. Claims having those limitations ultimately issued, though the examiner at that point was not the examiner who had rejected the earlier claim. Nonetheless, as Examiner Hodges recognized, the "capable of" language is not a patentable limitation.

Finally, the indefiniteness of claim 7 is exacerbated by the limitation that the recited EPO production levels be achievable "in 48 hours." The claims do not specify a particular 48-hour period. In other words, the cells satisfy the claims if, in any 48 hour period, they produce 100, 500 or 1000 "U of erythropoietin." Thus, determining infringement requires not only that the cells' EPO production be monitored under a limitless array of growth conditions but also at all times during their growth. Simply put, it is impossible for a potential infringer using cells to produce EPO at levels below those recited in the claims to know whether the cells have infringing production capability.

B. Amgen Cannot Meet its Burden to Prove Infringement of Claim 7

As a result of the infirmities of RIA and its use as claimed in the '349 patent, Amgen cannot show – as it must to prove infringement – that Roche uses cells capable of producing the specified number of "U of erythropoietin...as determined by radioimmunoassay."

As discussed above in section (IV)(A)(2), Amgen's own experts and documents confirm that RIA does not measure Units of biological activity and will measure materials in a test sample such as EPO fragments that are not "erythropoietin" according to this Court's claim construction. Claim 7 of the '349 patent is, therefore, meaningless in that it hinges on "erythropoietin" production recited, paradoxically, in terms of in vivo biological activity as

measured by RIA. An RIA, therefore, cannot determine whether cells used to produce EPO can produce the "U of erythropoietin" defined in the claims. Accordingly, Amgen cannot prove that Roche infringes claim 7 by using cells that satisfy claims 1, 2 or 3.

Nor has Amgen shown otherwise. As with all of the '349 claims, claim 7 expressly recites that the EPO production levels are in excess of specified levels as measured in "U of erythropoietin ...as determined by radioimmunoassay." A finding of patent infringement requires that the "accused device or method must embody each and every element of a [properly construed] claim." *Mass. Inst. of Tech. v. Lockheed Martin Global Telecomms., Inc.*, 251 F. Supp. 2d 1006, 1010 (D. Mass. 2003) (Young, C.J.); see *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538-39 (Fed.Cir.1991).

Roche does not use RIA to measure Units of EPO production of DN2-3α3 cells.[6] Amgen's experts, however, assert that "other data" reported by Roche and Chugai indicate that the production levels of the claims would be satisfied by Roche's DN2-3α3 cells. However, almost all of this "other data" does not employ an RIA. Moreover, all such data obtained by Roche is expressed in International Units (IU), though the term "U of erythropoietin" is not defined in the '349 patent as meaning International Units. As Amgen's Dr. Rathmann stated: "[u]nless the precise method to be used was defined, there would be no basis for stating international units." (Ex.. O at AM-ITC 00558660).

[6] Amgen has recognized that any attempt to prove infringement must utilize RIA as required by the claim. Amgen moved to compel production of Roche's cell line stating that it required "discovery of Roche's cell line to demonstrate infringement of its asserted claims," particularly pointing out that the '349 claims "require that the claimed vertebrate cells of capable of producing . . . units of EPO as measured by radioimmunoassay (RIA) . . . ." (Docket Index #223, Amgen Inc's Memorandum In Support Of Its Motion To Compel Production Of Roche's Cell Line And Related Documents at 1).

Apparently recognizing the ambiguity of "under suitable nutrient conditions," as it previously defined the phrase,[7] Amgen now asserts that claim 7 of the '349 patent "makes plain that the cells must produce the recited amount of EPO ***when grown in culture under the nutrient conditions employed in the accused process***." (D.I. 532, Amgen Inc.'s Memorandum In Support Of Its Motion For Summary Judgment That Dr. Lin's Asserted Claims Are Definite, Adequately Described, And Enabled at 9 (emphasis added)). Assuming, *arguendo*, that Amgen's interpretation is correct, this further indicates that Amgen has not met its burden of proof in showing that each and every limitation of the asserted claim has been met.

Amgen's proffered evidence of infringement is fatally flawed because the ***nutrient conditions*** Roche ***employs in the accused process*** was not specifically tested. Amgen's testing expert Dr. Kolodner confirmed that he employed different nutrient and cell culture conditions than Amgen accuses Roche of using. (Ex. BB at ¶¶ 12-13). Dr. Kolodner's procedures specified that he took samples from cells for analysis during a stage in their maintenance that Roche does not practice. (Ex. BB at ¶¶ 18-19, 22). Finally, in Dr. Kolodner observed that cell death occurred shortly after culturing began, which does not in any way match the conditions under which Roche carefully maintains cells derived from the DN2-3α3 cell line. (*Id.*). Simply put, Dr. Kolodner did not grow Roche's cells under the same conditions employed by Roche. As such, his data cannot prove infringement.

Moreover, and as discussed in detail above, the test itself – RIA – cannot determine whether the collected growth medium samples even contained "erythropoietin." As discussed above, an RIA assay will detect any substance that reacts with the antibody. There is no evidence that the material measured by Dr. Kolodner was all "erythropoietin." The material

[7] Ex. V at ¶ 50.

measured by Dr. Kolodner was an impure mix of substances found in the culture supernatant. The impurity of this mixture is illustrated by the complex process that Roche uses to first isolate then purify its product from the numerous impurities present in growth medium. Amgen has made no effort to determine whether "erythropoietin" was present at all in the samples they measured. For these reasons, Amgen's conclusion that cells, under different conditions, measuring an unknown substance that happens to be recorded in an RIA, cannot constitute proof of Roche's infringement of the process of claim 7 of the '349 patent.

V. CONCLUSION

For the reasons set forth above, the Court should grant Roche's motion for summary judgment that claim 7 of the '349 patent is invalid for indefiniteness and lack of written description and enablement. For substantially the same reasons, Amgen has failed to meet its burden of proving each and every limitation embodied in claim 7 has been met, and therefore Roche is entitled to summary judgment of noninfringement.

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Respectfully submitted,

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I hereby certify that a redacted version of this document was filed through the ECF system and was sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies were sent to those indicated as non-registered participants on June 22, 2007.

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