**UNITED STATES DISTRICT COURT**
**DISTRICT OF MASSACHUSETTS**

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

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

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Pursuant to Federal Rule of Civil Procedure 56, Plaintiff Amgen Inc. ("Amgen") hereby moves for summary judgment that:

Dr. Lin's asserted claims are not indefinite:

(1) Dr. Lin's recitation of "non-naturally occurring" glycoprotein products in Claims 3, 7-9, 11-12, and 14 of U.S. Patent No. 5,547,933 (the "'933 Patent" or "'933") would be understood by one of ordinary skill in the art to distinguish between EPO products that naturally occur in nature and those that are produced only through human intervention;

(2) Dr. Lin's recitation in Claim 7 of U.S. Patent No. 5,756,349 (the "'349 Patent" or "'349") of cells that 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," would be understood by an ordinarily skilled artisan to require: (a) the use of cells that produce in excess of 100 U of erythropoietin per $10^6$ cells in 48 hours; and (b) a radioimmunoassay in which an antibody and EPO sample are calibrated against a known EPO standard;

(3) Dr. Lin's recitation of "human erythropoietin" in various asserted claims of U.S. Patent Nos. 5,547,933; 5,756,349; 5,955,422; 5,441,868; and 5,618,698[1] would be understood by an ordinarily skilled artisan to include all of the allelic variants of the human erythropoietin amino acid sequence, including EPO products that are produced according to Example 10 of Dr. Lin's patents;

Written Description and Enablement:

(4) As a matter of law, Dr. Lin only needed to describe and enable his claimed inventions; he did not need to enable one of ordinary skill to make pegylated erythropoietin.

## I. INTRODUCTION

In past proceedings, the Court and the Federal Circuit have found "non-naturally occurring," "capable upon growth in culture," "units of erythropoietin . . . as determined by

[1] "Human erythropoietin" refers to the protein in '422 Claim 1 and '349 Claims 4-6 and 7 (to the extent that it depends on Claims 4-6). In all other asserted claims, "human erythropoietin" refers to a DNA sequence encoding human erythropoietin. *See* Ex. 3, U.S. Patent No. 5,547,933; Ex. 5, U.S. Patent No. 5,756,349; Ex. 6, U.S. Patent No. 5,955,422; Ex. 2, U.S. Patent No. 5,441,868; Ex. 4, U.S. Patent No. 5,618,698. All citations to exhibits herein refer to exhibits to the Declaration of Renee DuBord Brown in Support of Amgen Inc.'s Motion for Summary Judgment That Dr. Lin's Asserted Claims are Definite, Adequately Described and Enabled.

radioimmunoassay," and "human erythropoietin" in Dr. Lin's patent claims to be sufficiently definite to determine the metes and bounds of the claims that contain these limitations and sufficiently definite to determine whether such claims were infringed.

During the claims construction briefing in this case, Roche did not contend that "non-naturally occurring," "capable upon growth in culture," or "human erythropoietin" were indefinite. It was not until this Court rejected Roche's proposed constructions for these three terms that Roche began arguing that the terms were indefinite. Before then, Roche was happy to assert that the intrinsic record gave these terms a meaning that would advance either Roche's non-infringement arguments or invalidity attacks. Because Roche failed to raise these contentions in its claim construction submissions (the determination of definiteness is part of claim construction), it should be held to have waived them.

Nevertheless, Roche now asserts that the terms "non-naturally occurring," "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," and, incredibly, "human erythropoietin," have no definable meaning. Roche's position is not supported by the intrinsic record, its past positions at *Markman*, or this Court's past findings.

As Roche conceded in its *Markman* submissions, the Federal Circuit has already determined that "non-naturally occurring" means a product "not occurring in nature"[2] and serves as a negative source limitation to distinguish whether a product is obtained from a natural source (*e.g.*, urine, serum) or a non-natural source (*e.g.*, EPO obtained from genetically manipulated cells, or synthetically manufactured EPOs). Thus, there can be no legitimate dispute as to the meaning or scope of the term.

[2] Defs.' Mem. in Opp'n to Amgen Inc.'s Claims Construction Br. (Docket No. 322), App. B at 10.

The term "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," in the context of asserted of '349 Claim 7, is equally definite. There can be no legitimate dispute that the use of a radioimmunoassay (RIA) to measure the amount of EPO was well-known and well within the understanding of one of ordinary skill at the time of Dr. Lin's inventions. Neither is there a dispute that Dr. Lin described the RIA he used in his specification, or that one of ordinary skill could readily calibrate the results obtained from one RIA to the results obtained using a different RIA. Nor can there be any legitimate dispute that an alleged infringer would know how to determine whether the cells used in its process produced the required levels of erythropoietin (as measured by RIA) under the cell culture conditions used in the process. Under these circumstances, as a matter of law, '349 Claim 7 is definite.

As this Court has already found, "human erythropoietin" means "a protein having the amino acid sequence of human EPO, ***such as*** the amino acid sequence of EPO isolated from human urine."[3] Notably, Roche had advocated a claim construction that referred to the same amino acid sequence as the Court's construction.[4] Not only has the term "human erythropoietin" been considered and applied in prior litigations without qualm, but Roche has presented no evidence to show that one of ordinary skill in the art would fail to understand the Court's current construction. Since there is no legitimate issue of material fact as to the meaning of the term, Amgen is entitled to summary judgment on this defense.

Finally, while apparently conceding that Dr. Lin adequately described and enabled ordinarily skilled artisans to make and use recombinant erythropoietin, Roche nevertheless

[3] Ex. 1, 4/17/07 *Markman* Hearing Tr. at 23:17-39:10.

[4] Defs.' Opening Mem. in Supp. of Their Proposed Claim Construction (Docket No. 311) at 1 ("a glycoprotein having the ***amino acid sequence of erythropoietin isolated from human urine*** having the structure that would be produced in mammalian cells as of the invention date").

asserts that all of Dr. Lin's claims are invalid for failing to describe and enable how to make and use ***pegylated*** EPO. Once again, Roche's argument is a red herring. Just as the inventor of a tire need not describe every feature of a car that uses the inventor's claimed tire, Dr. Lin need not describe or enable the many different uses to which infringers — such as Roche — put his claimed EPO products. So long as Dr. Lin described and taught one of ordinary skill in the art how to make and use his claimed product — EPO — his claims satisfy the written description and enablement requirements of section 112.

## II. ARGUMENT

### A. Dr. Lin's claims are definite.

35 U.S.C. § 112, second paragraph, requires that a patent specification conclude with one or more claims "particularly pointing out and distinctly claiming subject matter which the applicant regards as his invention." The standard for assessing whether a patent claim is sufficiently definite to satisfy the statutory requirement is whether "one skilled in the art would understand the bounds of the claim when read in light of the specification."[5] As held by the Federal Circuit, § 112, second paragraph does not require that a claim be absolutely precise, only that its meaning be discernable.[6]

Whether a patent claim is definite is a question of law[7] that "is drawn from the court's performance of its duty as the construer of patent claims."[8] As such, the issue of definiteness is particularly susceptible to summary judgment.[9] Furthermore, both parties have moved for

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[5] *Exxon Res. & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001), *quoting Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

[6] *Exxon*, 265 F.3d at 1375.

[7] *See Atmel Corp. v. Info. Storage Devices, Inc.*, 198 F.3d 1374, 1378 (Fed. Cir. 1999).

[8] *Personalized Media Commc'n, L.L.C. v. Int'l Trade Comm'n*, 161 F.3d 698, 705 (Fed. Cir. 1998).

[9] *See Exxon*, 265 F.3d at 1376.

summary judgment on the definiteness of "non-naturally occurring"[10] and "human erythropoietin,"[11] indicating there is no issue of fact regarding these terms that cannot be resolved by summary judgment.

**1. The asserted '933 claims, each directed to "non-naturally occurring" products, are definite because one of skill in the art could readily understand it to be a negative source limitation.**

'933 Claim 3 and each of the asserted claims which rely on Claim 3 are directed to "non-naturally occurring" glycoprotein products:

> 3. ***A non-naturally occurring glycoprotein product*** of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.[12]

As already determined by the Federal Circuit, the term "non-naturally occurring" is a negative source limitation that "merely prevents Amgen from claiming the human EPO produced in the natural course."[13] This meaning is amply supported by the intrinsic record.

For example, when Amgen introduced the term "non-naturally occurring" to the claims that ultimately issued in the '933 Patent, Amgen made plain that the term was being added as a "negative limitation" to differentiate Lin's claimed invention from naturally occurring EPO products.[14] That this negative limitation was a negative ***source*** limitation is made clear by the

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[10] *See* Defs.' Mot. for Summ. J. That the Asserted Claims of the '933 Patent Are Invalid for Indefiniteness and Lack of Written Description (Docket No. 505).

[11] *See* Defs.' Mot. for Summ. J. That Claim 1 of the '422 Patent Is Invalid Under 35 U.S.C. § 112 (Docket No. 482).

[12] Ex. 3, '933 Patent, Cl. 3 (emphasis added).

[13] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) [hereinafter *Amgen/HMR II]*.

[14] Ex. 25, '933 Prosecution History, 12/20/95 Second Preliminary Amendment and Remarks at 6 (AM-ITC 00941549).

fact that a separate and distinct structural limitation ("having glycosylation which differs from that of human urinary erythropoietin") was added at the same time,[15] and by Amgen's contrasting use of the term "naturally occurring" erythropoietin to refer to EPO products that were produced or derived from nature.[16]

The specification likewise distinguishes between Lin's claimed recombinantly-produced products and those products that are produced without human intervention:

> ***Products of the invention, by virtue of their production by recombinant methods***, are expected to be free of pyrogens, natural inhibitory substances, and the like, and are thus likely to provide enhanced overall effectiveness in therapeutic processes ***vis-à-vis naturally derived products***.[17]

At *Markman*, Roche seemingly agreed.[18]

Applying the Federal Circuit's definition, an ordinarily skilled artisan would readily understand the metes and bounds of the asserted '933 claims by answering one simple question — what was the source of the glycoprotein product? If the glycoprotein product was obtained from a source that naturally contains EPO without human intervention, it is outside the bounds of the claim. If not, it may be within the bounds of the claim if every other limitation of the claim is met. Plainly, a product that is produced by a cell that has been genetically engineered through

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[15] *Id*. at 2 (AM-ITC 00941545).

[16] See Ex. 25, '933 Prosecution History, 6/5/89 Amendment Under Rule 116 at 4 (AM-ITC 00941168) ("All of the references cited by the Examiner in this rejection [Miyake, Chiba, Takezawa, and Sugimoto] relate to naturally occurring erythropoietin. *The claims of the subject invention related to erythropoietin which is produced through recombinant DNA techniques*."); *id*. at 6; Ex. 25, '933 Prosecution History 11/30/88, Strickland Declaration at ¶ 5 (AM-ITC 00941121). *See also*, Ex. 25, '933 Prosecution History, 6/2/88 Office Action at 4, 9 (AM-ITC 00941093, 1098) (wherein the Examiner similarly used the term "native" EPO to refer to EPO obtained from natural sources).

[17] Ex. 3, '933 Patent at 33:39-44 (emphasis added); *see also id*. at 8:16-21 (comparing "synthetic peptides" with naturally occurring proteins);

[18] Defs.' Opening Mem. In Supp. Of Their Proposed Claim Construction (Docket No. 311), App. A at 2 (adopting this Court's construction of "non-naturally" occurring" from the HMR/TKT

human intervention falls within the scope of the asserted '933 "non-naturally occurring" claims, and a party deriving its product from such cells would know this.

Roche seeks to confuse the issue by conflating its arguments regarding "non-naturally occurring" with the arguments raised in the HMR/TKT litigation regarding the term "human urinary erythropoietin" (in the context of the limitation "having glycosylation which differs from that of human urinary erythropoietin"). But the two claim terms are indisputably different. In the context of "human urinary erythropoietin," the issue was whether a skilled artisan could reasonably determine which of many different possible preparations of urinary EPO provided the benchmark against which to assess the recited differences in glycosylation or molecular weight. Here, the issue is whether a skilled artisan could determine if an accused glycoprotein product was obtained from a source that naturally contains the glycoprotein without human intervention.

Indeed, rather than supporting Roche's allegation of indefiniteness, the Federal Circuit's review of the term "non-naturally occurring," as it is used in the '933 Patent, supports the term's definiteness. In considering '933 Claim 1, the Federal Circuit assigned the term 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.[19] Under these circumstances, this Court and the Federal Circuit's past decisions demonstrate that the term "non-naturally occurring" is definite, not indefinite.

**2. One of ordinary skill in the art could readily determine the metes and bounds of Claim 7 of the '349 Patent.**

'349 Claim 7, as it depends from Claim 1, provides:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells [which can be propagated in vitro and which are capable upon growth in

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litigation.)

[19] *Amgen/HMR II*, 314 F. 3d at 1340-42.

> 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.][20]

Roche asserts that '349 Claim 7 is indefinite on two grounds: (1) one of ordinary skill could not know whether cells 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" because it asserts there are an "infinite" number of different cell culture conditions in which such cells could hypothetically be grown, and (2) one of ordinary skill could not know whether their cells met the requisite production levels since radioimmunoassay results depend on the reagents used and Dr. Lin's specification purportedly did not provide sufficient guidance regarding the identity of these reagents. As a matter of law, neither argument renders '349 Claim 7 indefinite.

**a. As used in '349 Claim 7, "capable upon growth in culture" is definite.**

In the context of '349 Claim 7, one of ordinary skill in the art, reading the entirety of the claim, would understand that he would need to grow the vertebrate cells of Claims 1-6 "under suitable nutrient conditions," and determine by means of radioimmunoassay whether the cells produce more than 100 Units of EPO in the medium of their growth per $10^6$ cells in 48 hours. If, under actual culture conditions, an accused process produces 100 Units or less of erythropoietin, the process would not literally infringe '349 Claim 7.

Roche nonetheless asserts that '349 Claim 7 is indefinite because the phrase "capable

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[20] Ex. 5, '349 Patent, Cl. 7 (incorporating Cl. 1, from which it depends). Claim 4, the other independent claim on which '349 Claim 7 depends, provides:

> 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

upon growth in culture" would require one of ordinary skill to conduct undue experimentation to determine whether his cells were capable of producing EPO at the recited levels under *any and all possible* cell culture conditions, not just those actually used in the accused process. Roche then asserts that because there are an infinite number of hypothetical nutrient conditions under which one could grow the cells, there is no way, short of undue experimentation, to show that a cell is not capable of producing EPO at specified levels under any conditions.

But Roche ignores the full context of the claim language, which expressly requires performance of the "step of culturing, under suitable nutrient conditions," not the hypothetical possibility of culturing under some undefined set of nutrient conditions. Whether Roche can hypothesize an "infinite" number of possible "nutrient conditions" for growing cells is simply irrelevant to the actual language of Claim 7, which requires a stated level of EPO production under the specific "nutrient conditions" actually used in the accused process:

> . . . ***the step of culturing, under suitable nutrient conditions, 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 . . .][21]

Considered as a whole, '349 Claim 7 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.

As a matter of policy, if Roche's attack on '349 Claim 7 were upheld, it could be generalized for any limitation based on capability, suitability, ability, or a host of other common properties that would seemingly require undue experimentation under an "infinite" number of possible conditions. But the terms "capable of" or "capable upon," in and of themselves, should

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radioimmunoassay.

[21] Ex. 5, '349 Patent, Cl. 7 (incorporating Cl. 1, from which it depends) (emphasis added). Claim 4, the other independent claim on which Claim 7 depends, recite "capable of."

not render a claim indefinite.[22] Indeed, a search of the United States Patent Office website reveals over 228,000 patents issued since 1976 containing claims that use the term "capable of," and 306 patents containing claims using the term "capable upon."[23]

Based upon the language of Claim 7 itself, as well as in the context of the specification, the limitation "capable upon growth in culture" appropriately prescribes the metes and bounds of '349 Claim 7.

**b. Reference to a radioimmunoassay in '349 Claim 7 does not render the claim indefinite.**

Before 1983-1984, it was known that cobalt chloride could induce the production of erythropoietin by the kidneys. Based on that observation, in the 1950's, in order to help standardize the results being reported by various laboratories studying various putative preparations of erythropoietin, a "unit" of erythropoietin activity was defined as that amount of erythropoietin activity equivalent to 5 micromoles of cobalt chloride in a test animal.[24] As different preparations of EPO became available over the subsequent years, rather than measuring EPO activity using cobalt chloride, an International Reference Preparation ("IRP") standard was agreed upon and such standards were administered and distributed, in part, by the World Health

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[22] *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 345 F.3d 1318, 1326-27 (Fed. Cir. 2003) (construing "capable of flexing" and concluding its simple, ordinary meaning "capable of bending" was an operative limitation). Biotechnology patents with similar language have also been successfully construed: "A process for producing human IGF-I comprising preparing a replicable expression vector capable of expressing the DNA sequence encoding human IGF-I in a prokaryotic host cell." *Genentech, Inc. v. Inamed Inc.*, 436 F. Supp. 2d 1080, 1084-85 (N.D. Cal. 2006).

[23] *See* www.uspto.gov (June 5, 2007). In particular, see Ex. 7, U.S. Patent No. 4,353,982, Claim 1, issued to Hoffmann-La Roche Inc., claiming a process for determining the amount of an enzyme, creatine kinase, in a sample using an antibody "***capable of*** immuno-reactively binding selectively one of the B or M subunits of the creatine kinase in the sample" (emphasis added).

[24] Ex. 8, W. Fried et al., "Studies on Erythropoiesis: III. Factors Controlling Erythropoietin Production," *Proc. Soc. Exp. Biol. Med.* 94:237-41 (1957); *see* Ex. 23, 2/14/07 Goldwasser Tr. at 50:20-52:10.

Organization.[25] The unitage for each successive IRP EPO standard was based on the original definition of "unit" and was thus defined indirectly by reference back to the erythropoietic activity of 5 micromoles of cobalt chloride.[26]

A "radioimmunoassay" (RIA), as referenced in the specifications and claims of the '349 Patent, is an assay procedure that has been used since the 1970's to measure the amount of EPO in a sample based on the reactivity of the EPO in the sample with an antibody raised against purified EPO. The results of an RIA to measure EPO in a sample have nearly always been reported by those working in the EPO field in terms of "units" or "mU" (1/1000 of a unit) of EPO.[27] Indeed, in 1981, Roche's expert on RIA issues, Dr. Zaroulis, published a paper describing an RIA for measuring EPO, in which he and his colleagues reported the results of his RIA in "mU" (*i.e.*, milli-units): "The RIA for EP described in this investigation, can detect 5 mU/ml of EP in the assay tube; the serum concentration of EP in normal individuals ranged from <18 to 81 mU/ml with a mean value of 20 mU/ml".[28] Roche's witnesses argue that "U[nits] of erythropoietin . . . as determined by radioimmunoassay" is indefinite, but neither they nor Roche have offered any contemporaneous evidence showing that one of ordinary skill (or anyone else)

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[25] *See* Ex. 22, 5/31/07 Goldwasser Tr. at 175:14-17.

[26] *See* Ex. 16, 5/17/07 McLawhon Tr. at 266:8-267:24.

[27] *See*, *e.g.*, Ex. 9, J.C. Egrie et al., "Development of Radioimmunoassays for Human Erythropoietin Using Recombinant Erythropoietin as Tracer and Immunogen," *J. Immunol. Methods*, 99:240 (1987); Ex. 10, C. Zaroulis et al., "Serum Concentrations of Erythropoietin Measured by Radioimmunoassay in Hematologic Disorders and Chronic Renal Failure," *Am. J. Hemtol.*, 11:91 (1981); Ex. 20, J. Garcia et al., "Radioimmunoassay of Erythropoietin: Circulating Levels in Normal and Polycythemic Human Beings," *J. Lab. Clin. Med.* 99:624-635 (1982); Ex. 21, P. Koeffler et al., "Erythropoietin Radioimmunoassay in Evaluating Patients with Polycythemia," *Annals of Internal Med.*, 94(1):44-47 (1981); Ex. 14, Sherwood & Goldwasser (1979), "A Radioimmunoassay for Erythropoietin," *Blood*, 54(4):891.

[28] Ex. 10, Zaroulis et al. (1981), "Serum Concentrations of Erythropoietin Measured by Radioimmunoassay in Hematologic Disorders and Chronic Renal Failure" *Amer. J. Hematol.* 11:85-92, at 85 (Abstract).

in 1983-84 would not have understood the meaning of "U[nits] of erythropoietin . . . as determined by radioimmunoassay."

While Roche argues that Dr. Lin's specification did not enable one of ordinary skill to perform a radioimmunoassay as recited in the '349 claims, there can be no legitimate dispute that the use of an RIA to measure EPO in a sample was well-known and well-understood by one of ordinary skill at the time of Dr. Lin's inventions.[29] In fact, Example 2 of Dr. Lin's specification exemplifies the procedure for conducting an EPO RIA referenced in the claims. That portion of the specification states in part:

> Radioimmunoassay procedures applied for quantitative detection of EPO samples were conducted according to the following procedures:
>
> An erythropoietin standard or unknown sample was incubated together with antiserum for two hours at 37° C. After the two hour incubation, the sample tubes were cooled on ice, and $^{125}$I-labelled erythropoietin was added, and the tubes were incubated at 0° C for at least 15 more hours. . . .[30]

Roche has argued that the availability of "multiple standards" in 1983 rendered Dr. Lin's claims indefinite, but one of ordinary skill in 1983-84 would have readily understood that whatever standard was to be used in an RIA to measure EPO in a sample would and could be calibrated against the IRP standard in use at the time.[31] Another Roche expert, Dr. James Fisher, published a paper in 1982 describing the calibration of two different EPO standards used in his RIA a purified urinary EPO standard and the IRP standard available at the time.[32] Indeed, Dr.

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[29] *See* Ex. 11, 5/24/07 Shouval Tr. at 200:2-6; Ex. 12, J. Garcia et al., "Radioimmunoassay of Erythropoietin," *Blood Cells*, 5:405-19 (1979); Ex. 14, J. Sherwood & E. Goldwasser, "A Radioimmunoassay for Erythropoietin," *Blood*, 54(4):885-93 (1979).

[30] Ex. 3, '933 Patent at 16:55-59.

[31] *See* Ex. 22, 5/31/07 Goldwasser Tr. at 162:1-24, 163:9-164:11, 179:4-20.

[32] Ex. 13, Arvind B. Rege, Jesse Brookins & James W. Fisher, "A Radioimmunoassay for Erythropoietin: Serum Levels in Normal Human Subjects and Patients with Hemopoietic Disorders," *J. Lab. Clin. Med.* 100(6):835, fig.5 (1982). ("The dose-response regression lines

Fisher and his colleagues demonstrated that the RIA dose-response curves for these two EPO standards, each of which had very different biological activities (their specific activities were 70,400 U/mg and 2 U/mg, respectively) could nonetheless be superimposed and thus calibrated to one another.[33] In sum, the prior art publications of Roche's own expert demonstrate that one of ordinary skill in the art would have understood how to measure the amount of EPO in a sample by RIA, calibrate the measurements to a known standard, and report the results of that assay in "units" of EPO.[34]

Notwithstanding these indisputable facts, Roche argues that '349 Claim 7 is indefinite because: (1) its reference to "units" of EPO must mean a measure of biological activity; and (2) the specification fails to define which EPO standard was used in the RIA reported in the specification. But, as readily acknowledged by Dr. Shouval, yet another Roche expert, "units of erythropoietin . . . as determined by radioimmunoassay" was readily understood by one of ordinary skill in the art in 1983:

> Q. Now, reading your abstract in 1983, would the person of ordinary skill in the art have been able to understand what was meant with reference to units of erythropoietin as measured by radioimmunoassay?
>
> A. It meant that the cells produced erythropoietin and that it can be measured by radioimmunoassay, which has a standard curve. And there was a reference which was a relative reference which suggests how much -- I mean, which gives you a semi-quantitative idea regarding the units of EPO as decided at that time by those who developed assay.
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> Q. So is it your view the person of ordinary skill in the art would

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with either IRP Ep (2 U/mg of solid) or highly purified Ep (700,400 U/mg of protein) as standards were superimposed (fig.5)." *Id.* at 834). In this paper, Dr. Fisher also reported the results of his RIA in "mU" (*i.e.*, milli-units). *See e.g.*, *id.* at figs.4, 5, 7, 9, and tbls.II-V.

[33] *Id.* at 840.

[34] *See, e.g.*, Ex. 14, J. Sherwood & E. Goldwasser, "A Radioimmunoassay for Erythropoietin," *Blood*, 54(4):891, tbl.3 (1979).

have understood that language that I just pointed to?

A. Easily.[35]

Roche's argument that the availability of different antibodies rendered Dr. Lin's recitation of RIA units indefinite is simply misguided. Different antibodies were used in different labs to perform the RIA, and then were "calibrated" to a known standard so that an "apples to apples" comparison could be made.[36] Consequently, Roche's assertion that the term "U of erythropoietin . . . as determined by radioimmunoassay" is indefinite because different results could be obtained if different EPO standards or antibodies were used to measure the Units of EPO is contrary to the common practice of those in the art at the time, including Roche's own experts, to calibrate their assays against a known standard. Summary judgment should be entered that Claim 7 of the '349 Patent is not indefinite.

**3. As construed by this Court, one of ordinary skill would have readily understood that "human erythropoietin" refers to the product having the same amino acid sequence as human erythropoietin.**

On April 17, 2007, the Court 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."[37] As more fully set forth in Amgen's *Markman* Brief, this construction is supported by the intrinsic record.

For example, as used in the specification, "erythropoietin" refers to polypeptides having the same sequence of amino acid residues as naturally occurring erythropoietin:

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[35] 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"); Ex. 15, 6/8/07 Gaylis Tr. at 273:16-275:12; Ex. 16, 5/17/07 McLawhon Tr. at 24:18-26:18.

[36] Ex. 22, 5/31/07 Goldwasser Tr. at 163:9-164:5.

[37] Ex. 1, 4/17/07 *Markman* Hearing Tr. at 23:17-39:10 (emphasis added). The Court took under advisement whether the term should include reference to glycosylation as well as human erythropoietin's amino acid sequence.

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or ***all of the primary structural conformation (i.e., continuous sequence of amino acid residues)*** and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.[38]
>
> According to the present invention, DNA sequences encoding part or ***all of the polypeptide sequence of human and monkey species erythropoietin (hereafter, at times, "EPO"***) have been isolated and characterized.[39]

The prosecution history of the '422 Patent similarly makes plain that "human erythropoietin" includes any polypeptide that has the same sequence of amino acid residues as EPO isolated from human urine:

> [H]uman erythropoietin is understood to include any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in other mammalian cells.[40]

"Human erythropoietin" also includes any naturally occurring allelic variations in the amino acid sequence of human EPO.[41]

Roche offered a similar construction for "human erythropoietin" at *Markman* except 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:[42]

> a glycoprotein having the amino acid sequence of erythropoietin isolated

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[38] Ex. 3, '933 Patent at 10:9-15 (emphasis added).

[39] Ex. 3, '933 Patent at 13:50-53 (emphasis added).

[40] Ex. 24, U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33) at 5 (AM-ITC 00899474).

[41] Ex. 3, '933 Patent at 21:11-19; 35:10-20; 35:27-39.

[42] 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." Defs.' Opening Mem. in Supp. of Their Proposed Claim Construction (Docket No. 311) at 2.

> from human urine having the same structure that would be produced by mammalian cells as of the invention date.[43]

Roche argued that its proffered definition "was supported by the patentee's definition and use of this term in the specification and the prosecution histories,"[44] and was consistent with the understanding of an ordinarily skilled artisan.[45] Having failed to persuade the Court to adopt their attempt to read both a source and temporal limitation into the term "human erythropoietin," Roche now asserts that the term is undefinable and without meaning to one of ordinary skill in the art.

Not only is this position inconsistent with Roche's arguments at *Markman*, but it also flies in the face of this Court's previous finding that the claims containing the term "human erythropoietin" were sufficiently definite to be found infringed.[46] The finding that Lin's "human erythropoietin" claims were infringed necessarily implies that the claims were also sufficiently definite in meaning and in scope to sustain a judgment of infringement — a legal determination that should also apply to an indefiniteness analysis under principles of stare decisis.[47]

Ignoring these facts, Roche attempts to revive the same 166 vs. 165 amino acid sequence argument that was thoroughly vetted in the HMR/TKT case. Roche argues that based on Dr. Lin's Figure 6, which depicts the DNA sequence for the human EPO gene and the amino acid sequence deduced from that genomic DNA sequence, "human EPO" should be construed to require 166 amino acids. In the alternative, Roche also argues that any 165 amino acid sequence set forth in the specification is erroneous. But neither argument renders the claim term "human

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[43] *Id.* at 1.

[44] *Id.* at 6.

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

[46] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 52-62, 165 (D. Mass. 2001) [hereinafter *Amgen/HMR I*]; *Amgen/HMR II*, 314 F.3d at 1347-50, 1358.

[47] *Wang Labs., Inc. v. Oki Elec. Indus. Co.*, 15 F. Supp. 2d 166, 175-76 (D. Mass. 1998).

erythropoietin" indefinite. Rather, Dr. Lin's specification makes plain that "human erythropoietin" refers to a protein having the same amino acid sequence as human urinary EPO and allelic variants thereto as well as proteins produced in a variety of recombinant cells using DNA encoding human EPO.[48]

The fact that Dr. Lin's description allows for some variation in the amino acid sequence of "human erythropoietin" does not render the term "human erythropoietin" indefinite. As the specification specifically contemplates, "human erythropoietin" may include proteins with an amino acid sequence that corresponds to allelic variants:

> Comprehended by the present invention are those various naturally-occurring allelic forms of EPO which past research into biologically active mammalian polypeptides . . . indicates are likely to exist. . . . Allelic forms of mature EPO polypeptides may vary from each other and from the sequences of FIGS. 5 and 6 in terms of length of sequence and/or in terms of deletions, substitutions, insertions or additions of amino acids in the sequence . . . .[49]

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.[50]

Example 10 of the specification, describing a method for producing "human erythropoietin," discloses products that have a 1-165 amino acid sequence.[51] The fact that "human

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[48] *See* Ex. 3, '933 Patent at 15:13-26. *See generally S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1367 (Fed. Cir. 2001) (the definiteness requirement of 35 U.S.C. § 112 is satisfied when an ordinarily skilled artisan would "understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification.")

[49] Ex. 3, '933 Patent at 35:17-31.

[50] Ex. 3, '933 Patent at 10:8-14.

[51] Ex. 19, 9/28/99 Decl. of Jeffrey K. Browne, Ph.D. Where a physical characteristic is inherent to an invention, a patent applicant who expressly discloses that characteristic completely only in a subsequent amendment is nevertheless entitled to the application's original priority date. *See, e.g.*, *Kennecott Corp. v. Kyocera*, 835 F.2d 1419, 1422-23 (Fed. Cir. 1987) (a product's existing physical structure is inherent and described when it is the inevitable result of a synthesis process

erythropoietin" is variously described in Dr. Lin's specification is entirely consistent with the fact that his specification and claims are directed to human erythropoietin and its naturally occurring allelic variants. The fact that "human erythropoietin" includes these variants is no basis for finding Dr. Lin's asserted claims to be indefinite.[52]

**B. As a matter of law, Dr. Lin need not describe and enable the production and use of peg-EPO.**

There is no question that Amgen's specification describes and enables one of ordinary skill in the art to make human erythropoietin as claimed in the '933 and '422 Patents.[53] Sidestepping this indisputable fact, Roche argues that because Amgen contends that pegylated EPO infringes Lin's EPO claims, Lin's claims must adequately describe and enable pegylated EPO products.[54]

This argument reflects a fundamental misunderstanding of the law of infringement and its intersection with the enablement and written description requirements. 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

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described in the specification); *Regents of the Univ. of N.M. v. Knight*, 321 F.3d 1111, 1122 (Fed. Cir. 2003); *Pall Corp. v. Micron Separations, Inc.*, 792 F. Supp. 1298 (D. Mass. 1992) (express language enumerating inherent properties does not introduce new matter).

[52] According to the legal arguments contained in Roche's Expert Reports, Roche's complaint is that Dr. Lin's specification provides multiple and erroneous definitions of "human erythropoietin." These allegations misapprehend the scope of Amgen's claims to "human erythropoietin."

[53] *Amgen/HMR II*, 314 F.3d at 1334-37. Enablement is a question of law based on underlying factual findings. *Id*. at 1313. Although the adequacy of written description is a question of fact (*id*. at 1330), the issue raised by Roche is purely a legal question, namely, whether Lin is required to describe his invention as claimed or, as advocated by Roche, whether he must also describe every feature of any product that incorporates his invention.

[54] Ex. 17, Defs.' Third Supp. Resp. & Objections to Pl. Amgen Inc.'s First Set of Interrogs. at 86. *See also* Ex. 18, Expert Report of Dr. Robert Langer (4/6/07) at ¶ 62.

product, elements such as PEG ***that are not recited in the claims***, does not negate infringement.[55] 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.[56]

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 enablement focuses only upon the claimed invention, not the accused product.[57] It is black letter law that a patent specification must describe and enable the full scope of the claimed invention.[58] However, "[t]he law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention."[59] Nor does it require that the specification enable all such embodiments.[60]

Cases such as *Amstar*[61] and *A.B. Dick*[62] applying the additional elements rule in the

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[55] *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1482 (Fed. Cir. 1984); ("Modification by mere *addition* of elements of functions, whenever made, cannot negate infringement without disregard of the long-established [] hornbook law . . . ."). *See also* Amgen's Mem. in Supp. of Its Mot. for Summ. J. of Infringement.

[56] 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.

[57] *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.").

[58] *Id.*; *see also AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1241 (Fed. Cir. 2003).

[59] *SRI, Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985).

[60] *Amgen/HMR II*, 314 F.3d at 1335-36.

[61] *Amstar*, 730 F.2d at 1482, 1484.

[62] *A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700 (Fed. Cir. 1983).

infringement context do not require that the patentee have described or enabled these unclaimed additional elements. In this context, as in other similar situations,[63] a patent may read on an accused product irrespective of whether the accused product contains additional features that are not described or enabled by the specification. Rather, just as the inventor of a tire does not need to describe or teach how to make an automobile that uses the tire, the only issue here is whether the specification describes and teaches how to make EPO. This issue has already been determined and as such is ripe for summary judgment.[64] As 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 each of the reasons set forth above, Amgen requests that: (1) each of Roche's allegations of indefiniteness of one or more of Dr. Lin's asserted claims be decided in Amgen's favor on summary judgment; and (2) Roche's argument that Dr. Lin's claims are not adequately described or enabled be rejected on summary judgment, insofar as Roche contends that Dr. Lin had to describe and enable the manufacture and use of peg-EPO.

[63] For example, under the doctrine of equivalents, equivalents do not have to be disclosed in the patent. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 37 (1997). In addition, after-arising technology does not need to be enabled. *See U.S. Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251-52 (Fed. Cir. 1989).

[64] *Amgen/HMR II*, 314 F.3d at 1330-37, 1358.

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Respectfully Submitted,

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