IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE, LTD, ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE INC., Defendants.	Civil Action No. 05-12237 WGY U.S. District Judge Young **ORAL ARGUMENT REQUESTED**

ROCHE'S OPPOSITION TO AMGEN'S MOTION FOR SUMMARY JUDGMENT THAT DR. LIN'S ASSERTED CLAIMS ARE DEFINITE, ADEQUATELY DESCRIBED AND ENABLED

Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky (*pro hac vice*)
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Christopher T. Jagoe (*pro hac vice*)
Kaye Scholer LLP
425 Park Avenue
New York, NY 10022
Tel. (212) 836-8000

Lee Carl Bromberg (BBO# 058480)
Timothy M. Murphy (BBO# 551926)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292

Counsel for Defendants
F. Hoffmann-La Roche, Ltd,
Roche Diagnostics GmbH, and
Hoffmann-La Roche Inc.

Dated: Boston, Massachusetts
July 5, 2007

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

I. INTRODUCTION

Defendants F. Hoffmann-La Roche, Ltd, Roche Diagnostics GmbH, and Hoffmann-La Roche Inc. (collectively, "Roche") respectfully submit this memorandum in opposition to Amgen's Motion For Summary Judgment That Dr. Lin's Asserted Claims Are Definite, Adequately Described And Enabled ("Amgen Motion"). Roche has already submitted its own motions for summary judgment alleging invalidity based on indefiniteness of '933 claim term "non-naturally occurring," '422 claim term "human erythropoietin" and '349 claim terms "capable of" and "U of erythropoietin . . . as determined by radioimmunoassay."[1] As to these claim terms, there are no factual issues.[2] To summarize:

● "Non-naturally occurring" is indefinite because, contrary to Amgen's assertions otherwise, it must impart structure to the claimed glycoprotein product or the '933 claims would have never been allowed over urinary EPO disclosed in the prior art. The only structural distinction disclosed in the patent or asserted by Amgen compares glycosylation of the claimed product with urinary EPO. This Court and the Federal Circuit have confirmed that urinary EPO is a "standardless standard." As such, the '933 claims containing this term are invalid for indefiniteness.

● "Human erythropoietin" is indefinite because, one of skill in the art, reading the Lin disclosure, would not be able to correctly ascertain the amino acid sequence of human erythropoietin and could not determine the proper scope of the claimed invention. The Court's construction defines "human erythropoietin" as "a protein ***having the amino acid sequence*** of human EPO, such as ***the amino acid sequence*** of EPO isolated from human urine." However, the patent's actual disclosure fails to include any accurate description of the sequence of amino acid residues possessed by EPO

[1] DI # 482 (Roche's Mot. for Summ. J. That Claim 1 of the '422 Patent Is Invalid under 35 U.S.C. § 112); DI # 539 (Roche's Motion for Summary Judgment That Claim 7 of Patent No. 5,756,349 Is Invalid under 35 U.S.C. § 112 & Is Not Infringed); DI # 505 (Roche's Mot. for Summ. J. That the Asserted Claims of the '933 Patent Are Invalid for Indefiniteness & Lack of Written Description).

[2] Roche agrees there are no issues of disputed fact regarding the definiteness of the three claim terms at issue in Amgen's motion, however, there may be issues of fact relating to claim terms not at issue in this motion.

isolated from human urine. Claims including this term according to the Court's claim construction are therefore invalid for indefiniteness.

- "Capable of" and "U of erythropoietin . . . as determined by radioimmunoassay" are indefinite because (1) a radioimmunoassay ("RIA") is incapable of distinguishing "erythropoietin" from materials that are not "erythropoietin," (2) "U of erythropoietin" has always been used to measure EPO biological activity which cannot be measured by RIA, and (3) numerous RIA standards were known at the time of the invention and each one would have reported different values for "U of erythropoietin" in a test sample. The patent provides no instruction as to which standard to use. Therefore, claim 7 of the '349 patent is invalid for indefiniteness.[3]

Contrary to Amgen's assertion that Roche was required to raise its indefiniteness defenses at the *Markman* Hearing or waive them, Roche was under no such obligation. In fact, patent law dictates that invalidity and claim construction are inextricably intertwined, suggesting that claim construction may in many cases be a necessary first step to any invalidity analysis, including indefiniteness.

Almost as an afterthought, Amgen also asks this Court to decide whether the asserted patents need to enable and describe "pegylated erythropoietin." Amgen slips this in, presenting it as a "question of law" to distract this court from fundamental factual issues that are in dispute in this case. Amgen is well aware from the long, tortured history of its patents in the Patent Office and Courts that the Lin patent claims are not entitled to cover everything that acts like EPO. The patent law is designed to encourage innovation. That is what Roche has done here. It has made a new molecule that acts *better* than EPO. Amgen seeks to reach beyond what it described and enabled through Dr. Lin's cloning of the gene encoding human erythropoietin to stifle innovation on the

[3] Pursuant to Rule 56f, Roche requires the opportunity to supplement its opposition to include testimony of Dr. Harvey F. Lodish. Dr. Lodish was made available for his deposition on July 3, 2007 and, as a consequence, his transcript is not yet available for citation.

wholly erroneous premise that its patents encompass everything that uses the amino acid sequence of erythropoietin as a starting material, regardless of how that sequence may be changed. This Court should not be deceived by Amgen's effort to recast the central factual dispute in this case as a "question of law" and should deny Amgen's motion.

II. ARGUMENT

A. An Indefiniteness Challenge Is Properly Raised After Claim Construction

Amgen's view that Roche's failure to raise its indefiniteness arguments during claim construction briefing constitutes a waiver of its right to now raise those issues is contrary to the law and to logic. An analysis of indefiniteness of a patent claim "is inextricably intertwined with claim construction."[4] To this end, the Court's claim construction in fact, frames the indefiniteness issues. This is illustrated by countless court decisions where indefiniteness is found after, and in many cases, as a consequence of claim construction.[5]

Moreover, even after claim construction it may not be immediately evident that a claim term as construed fails to inform one of skill in the art as to the bounds of the claims. Here, in the case of the claim term "human erythropoietin" as detailed below in section C, it was not until this Court construed "human erythropoietin" and Amgen's position as to what this term encompasses (as communicated by its experts) did it become clear that one skilled in the art would have *no*

---

[4] *Atmel Corp. v. Info. Storage Devices, Inc.*, 198 F.3d 1374, 1379 (Fed. Cir. 1999); s*ee Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1360 (Fed. Cir. 2004) ("An inventorship analysis, like an infringement or invalidity analysis, begins as a first step with a construction of each asserted claim to determine the subject matter encompassed thereby." (quoting *Trovan, Ltd. v. Sokymat SA*, 299 F.3d 1292, 1302 (Fed. Cir. 2002)); *see also ASM Am. Inc. v. Genus, Inc.*, No. C-01-2190-EDL, 2002 WL 1892200, at *15 (N.D. Cal. Aug. 15, 2002) ("The Court concludes that the Federal Circuit's statements that indefiniteness is intertwined with claim construction mean only that the Court must attempt to determine what a claim means before it can determine whether the claim is invalid for indefiniteness, and not that the Court must determine indefiniteness during the claim construction proceedings.").

[5] In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 91 (D. Mass. 2001) [hereinafter *Amgen I*], this Court construed the term "glycosylation which differs from that of human urinary erythropoietin" during *Markman* in late March and early April 2000. *See id.* at 92 (citing Tr. of Markman Hr'g, Vol. III at 102:18:23). Subsequently, during trial, this Court properly held the term "glycosylation which differs from that of human urinary erythropoietin" to be invalid for indefiniteness. *Id.* at 123-29. Also, in *Atmel*, in response to the defendants motion for summary judgment that a claim was indefinite, the court ruled "that it would be more efficient to construe the claims before ruling on validity." 198 F.3d at 1376.

understanding whatsoever as to the bounds of the '422 claim. In short, Amgen's position that Roche should have raised all indefiniteness issues at the claim construction hearing or forever waived its right to do so, is simply untenable.[6]

B. The Claim Limitation "Non-Naturally Occurring" Renders The Asserted Claims Of The '933 Patent Indefinite

By its motion filed June 14, 2007, Roche explained in detail why the term "non-naturally occurring" renders the claims of the '933 patent indefinite.[7] As detailed in that motion, Amgen's view that this term is simply a "negative source limitation" is contrary to the prosecution and litigation history[8] of the patent.[9] The Court's claim construction demonstrates that Amgen is wrong.[10] Thus, the product claimed cannot occur in nature.

Contrary to the position that it now takes, it is clear that Amgen intended and the Patent Office understood, "non-naturally occurring" to impart a structural limitation to the claimed product. During prosecution, in response to a prior art rejection by the Patent Office, Amgen amended the claims to recite "non-naturally occurring" and represented to the Patent Office that the limitation operates to "distinguish the subject matter claimed from all prior art reference relating to erythropoietin isolates."[11] Referring to this same amendment in its present motion, Amgen asserts that its addition of "the separate and distinct structural limitation (having glycosylation which differs from that of human urinary erythropoietin)" at the same time in that amendment, supports its

---

[6] In fact during claim construction the Court indicated its desire to construe claims objectively without regard to implications regarding validity. *See* April 17, 2007 Markman Tr. at pg. 82.

[7] Roche respectfully directs the Court's attention to the memorandum of law supporting that motion and incorporates those arguments by reference here. *See* DI # 506.

[8] *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003) [hereinafter *Amgen II*] ("[A] claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations.").

[9] It is Roche's view that if not indefinite, the '933 claims are invalid over prior art.

[10] *See* 7/3/07 Claim Construction Order 32 ("[A] glycoprotein (not occurring in nature) that is the product of the expression in a mammalian host cell of a DNA sequence that does not originate in the genemoe of the host, and which contains the genetic instructions (or a DNA sequence) encoding human erythropoietin.").

[11] *See* DI # 507 (Decl. of Howard S. Suh in Support of Roche's Mot. for Summ. J. That the Asserted Claims of the '933 Patent Are Invalid for Indefiniteness & Lack of Written Description, Ex. E at 7).

current view that "non-naturally occurring" imparts no structure. Quite the contrary is true. Amgen's point in fact, clearly confirms Roche's position. Issued claim 3 of the '933 patent reads as follows:

> 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.

Conspicuously absent from '933 claim 3 (or any of the claims asserted in this action) is any language regarding glycosylation. This raises the question, how (if at all) can the product of this claim be distinguished from the urinary erythropoietin prior art cited by the Patent Office? The simple answer is, Amgen must have intended and the Patent Office must have understood (whether correct or not) "non-naturally occurring" to impart some structural distinction over the prior art. This must be so because as discussed below, the law is quite clear that a source limitation without more cannot impart patentability to an obvious claim.

The process limitations set forth in the '933 claims cannot distinguish the claim over the prior art. The Federal Circuit agreed that "a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations."[12] This is consistent with another recent Federal Circuit decision which held that "a prior art disclosure of a product precludes a future claim to that same product, even if it is made by an allegedly novel process."[13] Therefore, the addition of the term "non-naturally occurring" to the claims of the '933 patent, to overcome prior art, had to reflect a physical or structural difference—not merely a

[12] *Amgen II* at 1354 n.20.
[13] *SmithKline Beecham Corp. v. Apotex Corp*., 439 F.3d 1312, 1319 n.7 (Fed. Cir. 2006).

difference in source or origin—between the claimed EPO products and the naturally occurring EPO in the prior art.[14]

However, the '933 patent recites one, and only one, physical or structural distinction between the claimed "non-naturally occurring" EPO glycoproteins and the EPO glycoproteins known in the prior art—their glycosylation.[15] This Court has established that glycosylation differences are indefinite and cannot be a valid basis for distinguishing claimed matter.[16] Claims which distinguished the claimed EPO from prior art human urinary EPO based on unspecified glycosylation differences were invalid for indefiniteness and lack of written description owing to the "enormous heterogeneity" of the glycosylation found in human urinary erythropoietin.[17] In invalidating these claims, this Court explained that

> different urinary erythropoietin preparations differ in their glycosylation, and because neither the patent nor the prior art provides clear guidance as to which human urinary EPO standard ought to be used, one of ordinary skill in the art would be unable to determine whether a particular erythropoietin has a glycosylation which differs from that of human urinary erythropoietin.[18]

Amgen is therefore collaterally estopped from arguing here that glycosylation is a valid basis for distinguishing between the non-naturally occurring EPO products of the claims and naturally occurring EPO.

Further, this Court specifically found that the glycosylation of human urinary erythropoietin varies, and thus concluded that the glycosylation of human urinary erythropoietin is a "moving target" and, therefore, a "standardless standard" by which to measure the claimed invention.[19] In

---

[14] Further confirming this, Amgen also attempted to claim "recombinant EPO" without any structural limitation during the prosecution of its U.S. Patent No. 5,955,422. This attempt was rejected by the Examiner as failing "to impose any definitive ***physical limitation*** on the claimed compositions." DI # 507 (Ex. G) (emphasis added).
[15] DI # 507 (Ex. A., col. 10:29-40).
[16] *Amgen I* at 91.
[17] *Id*. at 155.
[18] *Id.* at 156.
[19] *Id.* at 155. The Court found that

addition, Amgen's experts have submitted reports allegedly distinguishing non-naturally occurring EPO products from naturally occurring EPO on the basis of glycosylation alone. Amgen therefore agrees that glycosylation is the sole structural difference between the naturally occurring EPO of the prior art and the claimed EPO product.

Given that: (1) distinguishing claimed products from prior art based on the source or process but not the structure of the claimed products is not sufficient to make the claimed product patentable; (2) the only physical distinction between the claimed EPO products and EPO in the prior art that is taught by the patents is their glycosylation; and (3) this Court, as affirmed by the Federal Circuit, has already held that the glycosylation of naturally occurring EPO is a "standardless standard," it follows, therefore, that the asserted claims, which distinguish the claimed products as being "non-naturally occurring" must be invalid for indefiniteness.

C. The Claim Limitation "Human Erythropoietin" As Construed By The Court Is Indefinite When Read In Light Of The Specification Of The Patents-In-Suit

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."[20] The Court's construction expressly defines "human erythropoietin" by its ***particular sequence***. This definition is consistent with the level of specificity that is necessary to adequately define other polymeric

---

(1) the glycosylation of urinary erythropoietin has "enormous heterogeneity"; (2) different purification techniques [of urinary erythropoietin] . . . result in differing glycosylated erythropoietin populations; (3) . . . the ['933] patent does not identify which human urinary erythropoietin [should be the] standard . . . ; and (4) different urinary erythropoietin samples have different glycosylation. As a result, making comparisons between the glycosylation of recombinant EPO and that of human urinary EPO is virtually impossible. *Id.*

[20] *See* DI # 613 (7/3/07 Mem. & Order 15).

molecules like DNA.[21] The Court has thus established a boundary for claims containing this limitation based on a specified amino acid sequence.

Unfortunately for Amgen, these boundaries are nebulous due to their patent specifications.[22] The Lin patents do not disclose the accurate amino acid sequence of EPO isolated from human urine. Amgen repeatedly relies on the specification's disclosure of "erythropoietin" as "polypeptides having the same sequence of amino acid residues as naturally occurring erythropoietin . . . ."[23] The patent's actual disclosure, however, fails to include any description of the sequence of amino acid residues possessed by naturally occurring erythropoietin. Having read the specification, one of skill in the art would be unable to comprehend the actual sequence of "human erythropoietin," and could not determine the proper scope of the claimed invention. Claims including this term according to the Court's claim construction are therefore indefinite under 35 U.S.C. § 112 paragraph 2.

Contrary to Amgen's assertion, Roche's present argument regarding claims containing "human erythropoietin" is not simply a revival of the "166 vs. 165 amino acid sequence argument" disposed of in a prior litigation.[24] Human EPO was not even construed in the TKT case, nor did TKT raise 112 issues regarding the term as construed. Hence, the issues raised here have not been disposed of in prior litigation as Amgen suggests.

Amgen argues that one of ordinary skill in the art would understand that "human erythropoietin" as used in its patent specification is a polypeptide having the same amino acid sequence as human erythropoietin. This simply cannot be true. Human erythropoietin—the polypeptide found in human urine—is a specific polypeptide having a defined sequence of amino

---

[21] *See Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1206 (Fed. Cir. 1991); *see also In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

[22] Roche respectfully directs the Court's attention to the memorandum of law supporting Roche's Motion For Summary Judgment That Claim 1 Of The '422 Patent Is Invalid Under 35 U.S.C. § 112 and incorporates those arguments by reference here. DI # 483.

[23] *See* Amgen Mot. 14-15.

[24] *Id.* at 16.

acid residues of a specified length and order. In contrast, Amgen discloses numerous polypeptides in its patent specification,[25] and now alleges that all are "polypeptides of the invention" as stated in the patent specification. This incongruity highlights the flaw in Amgen's argument: rather than define or describe the precise sequence of human erythropoietin according to the Court's claim construction, the specification discloses a number of polypeptides, ***none*** of which are human erythropoietin as isolated from human urine.

As if to contradict the very clear position it took in its *Markman* briefing, Amgen now argues that "'human erythropoietin' also includes any naturally occurring allelic variations in the amino acid sequence of human EPO."[26] This is nothing more than a unjustifiable attempt to recapture material that it was not allowed to claim during prosecution of the Lin patents. Amgen now asks this Court to accept that "Dr. Lin's description allows for some variation in the amino acid sequence of 'human erythropoietin.'" Moreover, under Amgen's reasoning, "human erythropoietin" is an ever changing definition. As new allelic variations occur in nature every day, the scope of Amgen's claim would continually expand.

The *Kennecott Corp. v. Kyocera International, Inc.*[27] case Amgen cites in support of its flawed position is not applicable here.[28] In contrast, Amgen's experts understand that different cells can produce products having a variety of amino acid sequences.[29] Therefore, under no circumstances is production of 165-amino acid human erythropoietin an "inevitable result" of the process outlined in Example 10 of the patent specification.

---

[25] *See* DI # 485 (Ex. 1 at col. 29 l. 46; col. 31 l. 10; col. 34 l. 56 (table); col. 35 l. 28; col. 35 l. 49; col. 35 l. 57; col. 35 l. 59; col.35 l. 63; col. 36 l. 7).
[26] Amgen Mot. 15. An allele is any of a group of possible mutational forms of a gene. *See* Ex. I, Webster's II Dictionary (3d ed.).
[27] 835 F.2d 1419, 1422-23 (Fed. Cir. 1987).
[28] Amgen Mot. 17 n.51.
[29] *See* DI # 593 (Ex. 297 at 10-11); *see also* Ex. A, Masaaki Goto, et al., *Production of Recombinant Human Erythropoietin in Mammalian Cells: Host-Cell Dependency of the Biological Activity of the Cloned Glycoprotein*, *in* 6 Biotechnology 67 (1988).

Amgen's position is also illogical in that it contends that a single molecule—"human erythropoietin"—can be described by more than one sequence. This outrageous position is completely at odds with the Court's claim construction for the term "human erythropoietin." Moreover, Amgen's position is contrary to teachings of the Federal Circuit suggesting that the sequence of a DNA segment provides its precise definition, just as this Court has defined "human erythropoietin" in terms of its true sequence of amino acid residues.[30]

Amgen argues that the term "human erythropoietin" covers amino acid sequences such as the 165 amino acid sequence of EPO isolated from human urine—which Lin did not describe[31]—but also may potentially cover other amino acid sequences as well. To the extent the Lin specification provides examples of the amino acid sequence of human erythropoietin, those examples are wrong, contradict one another, and create hopeless confusion as to the amino acid sequence being claimed. As Amgen recognizes:

> 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 other mammalian cells.[32]

For at least the following reasons, one of skill in the art would be unable to determine what Amgen actually claims as "human erythropoietin" in claim 1 of the '422 patent:

- The amino acid sequence information disclosed in Example 1 of the Lin disclosure is not the amino acid sequence of human urinary EPO and does not disclose the complete amino acid sequence of human erythropoietin.[33]

---

[30] *Chugai*, 927 F.2d at 1206.

[31] *See* DI # 485 (Decl. of Krista M. Rycroft in Support of Roche's Mot. for Summ. J. That Claim 1 of the '422 Patent Is Invalid Under 35 U.S.C. § 112). Amgen admitted that neither Figure 6 nor any other portion of the specification meets the statutory written description requirement to support claiming the 165 amino acid sequence. *See* Ex. 4, Amgen's Post-Hearing Mem. at 5.

[32] Amgen Mot. 15 (internal citations omitted).

[33] Although Roche maintains that the sequence of human urinary EPO could have been obtained by a person of ordinary skill in the art in 1983/1984 if Dr. Goldwasser's EPO had been accessible, Amgen alleges that the sequence of EPO isolated from urine could not be obtained even with state of the art sequencing technology. *See* DI # 483 at 17-18.

- Examples 7 and 10 do not accurately disclose the amino acid sequence of human EPO as defined because both examples purport to produce human erythropoietin described by Figure 6, which expressly discloses a 166 amino acid sequence, not the amino acid sequence of EPO isolated from urine.[34]
- Examples 11 and 12 disclose products containing "an additional methionine amino acid residue (at position -1)" which is not found in the 165 amino acid sequence of EPO isolated from human urine and, therefore disclose that human EPO has a 167 amino acid sequence.[35]
- Example 12 discloses another amino acid sequence purported by Amgen to be human EPO in which the terminal methionone and the initial alanine (at position +1) are not present. Therefore, the 165 sequence disclosed in Example 12 has the +2 through +166 sequence, which is different than the 165 amino acid sequence of EPO isolated from human urine.[36]
- In the prosecution history, Lin argued that there actually were two other amino acid sequences for human erythropoietin (1) ***a 193 amino acid sequence*** of -27 to +166 and (2) ***a 113 amino acid sequence*** of +54 to +166.[37]

Taken together, claims containing the limitation "human erythropoietin" are invalid, and Amgen's motion for summary judgment on this topic should be denied.

D. Claim 7 Of The '349 Patent Is Invalid As A Matter Of Law On The Grounds Of Indefiniteness, Lacks Written Description And Lack Of Enablement

Roche moved this Court for summary judgment that claim 7 of the '349 patent is invalid because it contains a claim limitation that is indefinite, and lacks enablement and an adequate written description.[38] In its motion for summary judgment concerning the same claim, however, Amgen recasts and misstates Roche's indefiniteness arguments. As presented in summary form below, Roche's position is sufficient to not only defeat Amgen's present motion, but also to compel an award of summary judgment in its favor that claim 7 is indefinite.[39]

Roche's belief that claim 7 is indefinite is rooted in the Court's construction for "human erythropoietin," discussed *supra*, defined as a polypeptide having a specific sequence of amino acid

---

[34] *Id*. at 18.
[35] *Id.* at 18. *See also* DI # 485 (Ex. 14 ¶¶ 32-33; Ex. 15 ¶¶ 26-27; Ex. 1 at col. 29:42-45).
[36] *See* DI # 483 at 18; DI # 485 (Ex. 1 at col. 32:10-17).
[37] *See* DI # 483 at 18; DI # 485 (Exs. 9-10 at 35-37).
[38] *See* DI # 539.
[39] The arguments are fully presented in DI # 540 (Roche's 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).

residues.[40] In light of this definition, Roche set forth three separate bases for indefiniteness of claims containing the limitation "U of erythropoietin . . . as determined by radioimmunoassay."[41] First, the definiteness requirement cannot be fulfilled because radioimmunoassay ("RIA") is incapable of distinguishing "erythropoietin" from materials that are not "erythropoietin."[42] Second, "U of erythropoietin" always has been a measure of EPO biological activity that cannot be measured by RIA.[43] Third, many standards for RIA were known at the time of the invention, each of which would have reported different values for "U of erythropoietin" in a test sample.[44] Therefore, the claim limitation "U of erythropoietin . . . as determined by radioimmunoassay" is inherently ambiguous.[45]

These claims are also indefinite because they are directed to cells "capable" of producing EPO without specifying the "suitable nutrient conditions" under which cells should be cultured to evaluate their capacity for production. For failing to specify these conditions, a cell may be "capable" of producing the specified amount of EPO today and infringe the claim, but not "capable" of doing so tomorrow and not infringe. Under this shifting standard, it is impossible for one practicing in this art to determine whether vertebrate cells can be used and not infringe claim 7.

For each of these reasons, claim 7 of the '349 patent is not "sufficiently precise to permit a potential competitor to determine whether or not he is infringing."[46] Roche respectfully requests this

---

[40] *See* DI # 540, Section IV.
[41] DI # 540 at 7-8.
[42] *Id.* at 7-10.
[43] *Id.* at 10-11.
[44] *Id.* at 11-14.
[45] S*ee Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1341 (Fed. Cir. 2003); *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993) (affirming indefiniteness where one of skill in the art could not determine whether a given compound was within the scope of the claims). Indefiniteness often arises when the claim language is "not sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton*, 5 F.3d at 1470; *see Halliburton Energy Servs., Inc. v. MI, LLC*, 456 F. Supp. 2d 811, 817 (E.D. Tex. 2006); *Semmler v. Am. Honda Motor Co.*, 990 F. Supp. 967, 975 (S.D. Ohio 1997).
[46] *Amgen II* at 1342 (quoting *Morton*, 5 F.3d at 1470).

Court deny Amgen's motion and grant its co-pending motion for summary judgment that claim 7 is invalid for indefiniteness.

The arguments found in Amgen's motion do not in any way effect these conclusions. Amgen argues that EPO standards were all "based on the original definition of 'unit' and unit was thus defined indirectly by reference back to the erythropoietic activity of 5 micromoles of cobalt chloride."[47] This fact is irrelevant to this motion. The important point ignored by Amgen is that the Unit ("U") is a measure of biological (here, "erythropoietic") activity. Similarly, the fact that different standards could be calibrated to one another is inconsequential to the relevant inquiry: whether the test specified by the claim can determine the claimed biological activity of a sample.[48] Amgen's own experts confirm that it cannot because biological activity is not measured by RIA.[49]

Amgen's argument that RIA measurements could be reported "in terms of 'units' or 'mU' (1/1000 of a unit)" says absolutely nothing about whether the substance measured in the test sample was "erythropoietin" as construed by the court. On the contrary, Amgen's own experts confirm that RIA does not necessarily detect "erythropoietin" in its entirety, and in fact, could recognize "relevant portions" of EPO including EPO fragments.[50] Simply put, even if one of skill could, with certain assumptions, record a value for "units" of EPO using RIA, that test could not give confirmation of whether the sample contained "erythropoietin," let alone "U of erythropoietin" as required by the claims. Amgen's argument merely refuses to consider the claim limitation as a whole.

---

[47] *See* DI # 532 at 11; Ex. B, 5/17/07 McLawhon Depo. Tr. 266:8-267:24.

[48] Amgen's discussion of the International Reference Program only underscores the indefiniteness of its claims. (Amgen Mot. at 10). In a document produced by Amgen in this litigation, its then CEO George Rathman stated: "[Amgen] should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units until we can establish an excellent correlation with international units. I do not believe such correlation exists today . . . I think we have also been careless with respect to what is the precision or uncertainty (accuracy) of our data . . . I think we should understand how any standard can deviate from 'parallelism' trying to relate to international units." DI # 542 (Suh Decl., Ex T. at AM-ITC 00558618). Apparently, Amgen was not using International Units that it asserts were the norm at the time.

[49] *See* DI # 540 at 10-11; DI # 542 (Decl. of Howard S. Suh in Support of Roche's Mot. for Summ. J. That Claim 7 of Patent No. 5,756,349 Is Invalid under 35 U.S.C. § 112 and Is Not Infringed, Ex. E at 50:20-51:21, 52:7-16, 56:1-6; Ex. F ¶ 75; Ex. J at 133:24-25).

[50] *See* DI # 540 at 7-10; DI # 542 (Ex. J at 151:18-152:8, 220:4-221:9).

Therefore, one of skill in the art at the time of the invention reading the claims as set forth in the '349 patent is faced with a conundrum. That skilled artisan would understand the term "U of erythropoietin" but also understand that measure of biological activity could not be "determined by radioimmunoassay." Or, even if, as Amgen asserts, RIA can determine "U of erythropoietin," one of skill in the art would understand RIA measures other species that are not "erythropoietin" as this Court has construed it, rendering the term "erythropoietin" itself insolubly ambiguous and the entire limitation indefinite.

Because there are no restrictions on the "suitable nutrient conditions" cells according to claims 1-6 can be cultured, claim 7 covers production of "erythropoietin" 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." Even if "U of erythropoietin" could be determined by RIA, which it cannot, the claim fails to set forth the bounds of the claimed invention and is indefinite. Amgen's argument that many other claims contain the claim term "capable of" or "capable upon" is without import to the present analysis because here there is no information on whether the claimed matter is "capable" of performing a ***definite*** act in accordance with the requirements of 35 U.S.C. § 112 ¶ 2.

Taken as whole, the record is clear that the claim limitation "U of erythropoietin . . . as determined by radioimmunoassay" is indefinite because of ambiguity associated with measuring "erythropoietin" or "U of erythropoietin" with RIA. Furthermore, claims covering vertebrate cells that are "capable" of producing erythropoietin without specifying the conditions for testing their capacity lack a fixed guidepost that can establish whether a given cell falls within the claims' scope. For these reasons, the Court should deny Amgen's motion and grant Roche's motion for summary judgment that claim 7 is indefinite.

E. Amgen's Claims Cannot Validly Encompass Analogs, Derivatives Or Other New Molecules

Amgen attempts to obscure the multiple factual issues that its motion raises by misstating the enablement and written description issues that its motion raises. The issue here is not whether Amgen needs to enable or describe elements that are not recited in the claims. The issue is what may Amgen properly encompass within the scope of its claims. The Patent Office and the courts have found that Dr. Lin's success in cloning the gene encoding human erythropoietin does not entitle it to claim all molecules with "EPO-like" activity. Amgen wants to do an end-run around this fact by asserting that its claims encompass any molecules that may have used the amino acid sequence of EPO as a starting material. Amgen's position simply seeks to recapture claim scope that the Patent Office and the courts found Amgen not to be entitled to.

Since Amgen's motion attempts to trivialize the irreversible chemical synthesis that Roche uses to produce CERA, certain facts are relevant at this juncture.[51] First, as admitted by Amgen's own experts, this is *not* a situation involving an added element. All of the amino acid residues that define human EPO are not found in CERA because hydrogen atoms have been chemically substituted on certain amino acids to create new, synthetic amino acid residues.[52] These new, synthetic amino acids are neither described nor enabled by Amgen's patents. Moreover, chemical molecules are not mechanical devices. The chemical reaction that produces CERA, which replaces a hydrogen atom on one of the amino acid residues that define human EPO with literally hundreds of

[51] *See* DI # 588 (Defs.' Opp'n to Amgen's Mot. for Summ. J. of Infringement of '422 Claim 1, '933 Claim 3, & '698 Claim 6).

[52] *See* Ex. C, Harvey Lodish et. al., *Molecular Cell Biology* 43 (6th ed. 2008) ("Although cells use the 20 amino acids shown in Figure 2-14 in the *initial* synthesis of proteins, analysis of cellular proteins reveals that they contain upward of 100 different amino acids. Chemical modifications of the amino acids account for this difference."); s*ee also* DI # 593 (Decl. of Keith E. Toms in Support of Defs.' Opposition to Amgen's Mot. for Summ. J. of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6, Ex. 287 at 235, 238).

carbon atoms and oxygen atoms is not a mere "addition," but rather, a "substitution"[53] that creates a new compound.[54] In fact, Amgen's experts in this litigation agree that there are only twenty natural amino acids.[55] Each of these has a common core, but it is the side chains that make them unique.[56] Changing the side chain of an amino acid makes a new amino acid.[57] In the case of CERA, those changes result in new, synthetic amino acids that do not occur in nature.[58]

With the issues now properly framed, the flaws in Amgen's position on written description and enablement argument are obvious.

1. Amgen Is Not Entitled To Claim EPO Analogs And Synthetic Polypeptide

Paragraph 1 of § 112 "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art . . . . 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."[59]

Here, the proper scope of Amgen's claims is delineated by the prosecution and litigation history of these patents. Over the years of prosecuting the Lin patent family, Amgen's attempts to secure claims to "synthetic polypeptides" and fragments of EPO were repeatedly rejected by the Patent Office. Nonetheless, Amgen seeks in this litigation to cover a molecule that is outside the scope of the claims that the Patent Office, this Court and the Federal Circuit deemed it to be entitled.

---

[53] In *Lilly*, the Federal Circuit found that substitution of a hydroxy group with a chlorine group, resulted in a new compound. 82 F.3d at 1570, 1573, 1577.
[54] Klibanov Decl. ¶¶ 94, 104, 105, 114-19; Jorgensen Decl. ¶ 138; DI # 593 (Ex. 273 ¶ 30).
[55] *See* Ex. C, Lodish, *supra* note 52, at 41-43.
[56] *Id.* at 41.
[57] *Id.* at 43.
[58] Klibanov Decl. ¶ 143.
[59] *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970).

Specifically, during the prosecution of Application No. 675,298, which is the parent application to all of the patents-in-suit, the Patent office rejected Amgen's claims to DNA sequences "coding for a polypeptide fragment or ***polypeptide analog of naturally-occurring erythropoietin***" as being indefinite in violation of 35 U.S.C. § 112.[60] Amgen eventually cancelled its EPO analog claim in favor of a new narrower claim 110.[61] New claim 110, which eventually issued as claim 7 of the '008 patent, read:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence ***encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin*** to allow possession of the biological property of causing bone marrow to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.[62]

However, even this narrower claim was held invalid by the Federal Circuit for lack of enablement.[63] There, the Court stated:

> Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.[64]

Therefore, not only did Amgen surrender its claim to EPO analogs based on rejections by the Patent Office, but Amgen's replacement of this claim with a narrower claim was later found to be invalid for lack of enablement by this Court and the Federal Circuit.

---

[60] *See* Ex. D at 100, November 30, 1984, Application No. 06/675,298 (emphasis added) and Ex. E at 4-5, June 16, 1986, Office Action, 06/675,298-8.
[61] *See* Ex. F at 14-15, July 10, 1987, Amendment and Reply, 06/675,298-20) ("In order to expedite prosecution of this application [sic] has reconstituted prior claims 77 and 96 as new claim 110.").
[62] *Id*. at 6 (emphasis added).
[63] *Chugai*, 927 F.2d at 1214.
[64] *Id*. at 1214.

Amgen additionally abandoned claims to "synthetic polypeptides" during the prosecution of the '933 patent. Amgen sought claims to a "synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6 . . . and having a biological property of naturally-occurring human erythropoietin."[65] The Patent Office rejected this and similar claims to "synthetic polypeptides" stating:

> Claims to "synthetic polypeptides" are not enabled by this disclosure. "Synthetic," as opposed to "recombinant," is an art recognized term which indicates a chemically derived rather than genetically engineered protein. No support for chemical synthesis of EPO or EPO fragments is shown by this disclosure.[66]

Similarly, Amgen surrendered claims to proteins "sufficiently duplicative" of EPO during prosecution of the '933 patent. Amgen tried unsuccessfully to obtain claims to erythropoietin analogs "sufficiently duplicative of that of naturally occurring human erythropoietin."[67] The PTO rejected this claim pursuant to 35 U.S.C. § 112 ¶¶ 1 and 2, on grounds of nonenablement and indefiniteness.[68] Amgen eventually withdrew these claims.

Clearly, the Patent Office and the Courts have considered the scope of claims to be accorded to Amgen based on Dr. Lin's cloning of the human EPO gene and determined that the specification does not enable or describe claims to analogs, derivatives and synthetic molecules. Amgen should therefore be estopped from asserting that its claims encompass such molecules now.

2. Pegylation Techniques Were Desired But Unpredictable And Difficult To Obtain As Of 1983/1984

Amgen does not refute Roche's position that the Lin patents do not enable or describe pegylation of proteins. There can be no dispute that the Lin specification is utterly devoid of *any*

[65] DI # 593 (Ex. 1 at 102).
[66] Ex. G, 07/113,178 application file history, Paper 4, 6/2/88 Office Action at 5.
[67] DI # 593 (Ex. 2 at 1).
[68] DI # 593 (Ex. 3 at 3).

mention of the reagents used in protein pegylation or pegylation methods. Thus, it is not surprising that Amgen does not contend that the Lin patents enable or describe pegylation.

Moreover, the evidence in this case establishes that one of skill in the art, in 1983/1984 when the Lin specification was filed, would not have been able to synthesize a pegylated protein without undue experimentation.[69] As established by scientific publications in this time frame, the science of pegylation was in its infancy, achieving a useful pegylated protein was quite unpredictable and would have required undue experimentation to achieve.[70] In fact, Amgen's own scientists and experts have conceded that in the relevant time frame (and even today) the field of pegylation was fraught with uncertainty.

Pegylation procedures employed during the late 1970s and 1980s were plagued by difficulties, including restriction to PEGs with low molecular weights, relatively unstable activated PEGs, and lack of selectivity in protein modification.[71] This gave rise to impure and heterogeneous substances that were difficult to purify.[72] Moreover, PEG molecules widely vary in structure and molecular weight.[73] There were many uncertainties in the art of pegylation in the mid-1980's that had to be experimentally determined without guidance from the art.[74] This uncertainty in the art of

---

[69] 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). Further, where the desired product is a known concept in the art but difficult to obtain, an inventor must have disclosed how to make and use the product to assert coverage under the scope of the patent. *See Plant Genetic Sys. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1340-41 (Fed. Cir. 2003).

[70] According to the Federal Circuit:

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

[71] Klibanov Decl. ¶ 148.

[72] *Id.*

[73] *Id.* ¶139.

[74] *Id.* ¶¶ 145-46.

pegylation continued throughout the 1990s and was still considered to be a developing technology in 2006.[75]

Even Amgen's witnesses acknowledge the difficulty in successfully reacting PEG reagents with proteins. For example, Dr. Lin stated in his deposition that to determine whether a PEG modified protein was active "you had to do it yourself to see if the end product that you modified—the way you did it—would be active or not. You had to check it out, experimentary [sic]".[76] In addition, both Dr. Elliot, an Amgen scientist, and Mr. Boone, Amgen's spokesman in this litigation on Amgen's efforts to create a product from the reaction of erythropoietin and PEG reagents, have stated that pegylation is unpredictable and there is no way to know what properties the product of the pegylation reaction will have unless you perform the experiments.[77]

Underscoring this reality, when applying for a patent for its own pegylated product in 2000, pegylated NESP (Novel Erythropoietin Stimulating Protein), Amgen called the results of the pegylation reactions "surprising."[78] In addition, Amgen argued at the Patent Office that its PEG-NESP was novel and not obvious and that pegylation was unpredictable, stating that "not all proteins respond equally to PEGylation and there is no guarantee of improved performance."[79]

III. CONCLUSION

Based on the foregoing, Roche requests that Amgen's motion for summary judgment that Dr. Lin's asserted claims are definite, adequately described and enabled be denied.

---

[75] DI # 593 (Ex. 90 at 205; Ex. 121 at 215; Ex. 222 at 644).
[76] DI # 593 (Ex. 225 at 94:2-95:12, 100:9-22). Dr. Lin also stated in his deposition that he was aware of pegylation in November 1984, and that pegylation technology had been described in the literature, yet he did not disclose it in his patents. *Id.* at 91:19-25; *see* Ex. H Lin Tr. (3/29/07) 304:12-305:5).
[77] DI # 593 (Ex. 94 at 46:10-22; 93:1-10; 94:21-95:4; 96:12-21; Ex. 104 at 198:12-199:11.).
[78] DI # 593 (Ex. 52, U.S. Pat. No. 6,586,398 at col. 2).
[79] DI # 593 (Ex. 27 at 5).

Dated: July 5, 2007
Boston, Massachusetts

Respectfully submitted,

F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

By their Attorneys,

/s/ Nicole A. Rizzo

Lee Carl Bromberg (BBO# 058480)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
Kimberly J. Seluga (BBO# 667655)
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292
nrizzo@bromsun.com

Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky *(pro hac vice)*
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Peter Fratangelo (BBO# 639775)
Vladimir Drozdoff (*pro hac vice*)
David L. Cousineau (*pro hac vice*)
KAYE SCHOLER LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836-8000

CERTIFICATE OF SERVICE

I hereby certify that the 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 the above date.

/s/ Nicole A. Rizzo
Nicole A. Rizzo