UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN INC.'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 3, AND '698 CLAIM 6

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I. INTRODUCTION

Roche is seeking approval from the U.S. Food and Drug Administration ("FDA") to import for sale and sell a pharmaceutical product called Mircera to treat anemia of chronic kidney disease, an indication for which Amgen's Epogen® (epoetin alfa) and Aranesp® products are already approved and in use. The active drug substance in Mircera is "methoxy polyeythylene glycol-epoetin beta," which is also known as "peg-EPO." As its name suggests, "peg-EPO" comprises recombinant human erythropoietin (epoetin beta) and methoxy polyethylene glycol (peg). As Roche's chief scientist responsible for pre-clinical development succinctly acknowledged, "EPO is one part of CERA."[1]

By this Motion, Amgen seeks summary judgment that Roche's importation or sale of Mircera will literally infringe '422 Claim 1, '933 Claim 3, and '698 Claim 6.[2] As demonstrated below, there is no genuine issue of material fact that Mircera literally satisfies all of the limitations of the claimed products of '422 Claim 1 and '933 Claim 3 as construed and defined by the Court. There is also no dispute that Roche uses the process claimed in '698 Claim 6 to make EPO.

The only dispute regarding infringement is legal, not factual, and does not preclude summary judgment. That dispute is whether the attachment of peg to Lin's claimed recombinant human EPO circumvents infringement of Amgen's claims. The answer, as a matter of law, is no.

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[1] Ex. 49 at R004052565. Over time, presumably in anticipation of litigation, Roche instructed its employees to stop using the term "peg-EPO" in favor of a new name "CERA." *See also* Ex. 32 at R10-002933823; Ex. 69 at R003920864. All cited exhibits are attached to the Declaration of Katie J.L. Scott in Support of Amgen Inc.'s Motion for Summary Judgment of Infringement of '422 Claim 1, '933 Claim 3, and '698 Claim 6.

[2] The "'422, '933, and '698 patents" refer to U.S. Patent Nos. 5,995,422; 5,547,933; and 5,618,698, respectively.

Roche cannot avoid infringement of '422 Claim 1 and '933 Claim 3 merely by adding an additional element to Lin's claimed products. The relevant inquiry is whether the claim limitations are satisfied, not whether Roche's product has structure in addition to the structures claimed by Lin. In accordance with this Court's claim construction, the product of '422 Claim 1 and '933 Claim 3 is defined by the presence of a specific amino acid sequence and the presence of glycosylation imparted by the source from which the claimed products are obtained, not the presence or absence of other structures such as peg. Because the product Roche seeks to import or sell in the United States satisfies all of the limitations of '422 Claim 1 and '933 Claim 3, its attachment of peg to EPO is legally irrelevant.

With respect to the process of '698 Claim 6, no genuine dispute precludes judgment that Roche will infringe this claim as well. The fact that Roche practices Lin's process outside the United States does not shield Roche from liability because Roche will import the product of that process into the United States in its Mircera product in a manner that literally infringes 35 U.S.C. § 271(g). Roche undeniably uses Amgen's claimed process to make the EPO contained in Mircera. Section 271(g) protects U.S. patentees against off-shore infringement of their process claims if an imported product incorporates the product of their claimed process, unless the product of the claimed process is "materially changed by subsequent processes" or constitutes "a trivial and non-essential component" of the imported product.

Roche does not even attempt to argue that the EPO in peg-EPO is a "trivial" or "non-essential" component of Mircera. Without the EPO in peg-EPO, Roche's product would be therapeutically useless. Nor is the human EPO in Roche's peg-EPO changed, much less materially changed, from the product of Lin's claimed process. This Court properly defined "glycosylated erythropoietin polypeptide" by its amino acid sequence and the presence of

attached carbohydrate structures.[3] According to Roche's submission to the FDA, the amino acid sequence and carbohydrate structure of EPO are not changed by pegylation: "Both EPO starting material and RO0503821 [peg-EPO] have the identical amino acid sequence and composition of the carbohydrate moiety."[4] Thus, based on Roche's own admissions, the EPO in Roche's peg-EPO is "identical" in all relevant aspects to the EPO produced by Lin's claimed process.

Roche argues that the addition of peg to EPO creates a "new molecule," one that is substantially different from EPO. In support of this argument, Roche points to the peg moiety it attaches to Lin's claimed EPO, not to any change in the structure or function of the EPO itself. In doing so, Roche ignores the correct legal inquiry: was the product of the claimed process materially changed in the imported product? The fact that structure has been added to the product of Lin's claimed process is not a legally relevant change to the product of the process as defined by the Court, much less a material change. Since the EPO in peg-EPO is not changed in a legally relevant way, and is not a "trivial and non-essential component" of Mircera, summary judgment of infringement of '698 Claim 6 should also be granted.

II. STATEMENT OF FACTS[5]

Because Mircera is a drug, Roche can only sell it in the United States if it is approved by the FDA. The FDA requires full disclosure of the chemical composition of peg-EPO and the process used to make peg-EPO. Amgen bases this motion upon Roche's characterization of its product and manufacturing process to the FDA. Roche cannot dispute its past representations.[6]

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[3] Ex. 40, 4/17/07 *Markman* Tr. 91:18-92:10.

[4] Ex. 4 at ITC-R-BLA-00004027.

[5] Amgen has submitted a Separate Statement of Undisputed Material Facts in support of this Motion. Background regarding the science underlying EPO, peg-EPO, and Roche's manufacturing process can be found at Lodish Declaration ¶¶ 13-70.

[6] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 121 (D. Mass. 2001) ("A

Mircera is a pharmaceutical composition[7] containing pegylated epoetin beta ("peg-EPO"; Roche code name "RO0503821") and a pharmaceutically acceptable diluent.[8] Epoetin beta is a 165 amino acid recombinant human EPO glycoprotein with the identical amino acid sequence as the human recombinant EPO first disclosed and produced by Dr. Lin in Example 10 of his patent. The only difference between Lin's recombinant human EPO produced by Example 10 of the specification and the EPO in peg-EPO is the attachment of a peg moiety to the EPO protein via a single chemical bond.[9] In its effort to gain FDA approval, Roche admitted that the addition of peg changes neither the amino acid sequence nor the glycosylation of EPO:

> Both EPO starting material and RO0503821 have the identical amino acid sequence and composition of the carbohydrate moiety.[10]

Nor does Roche's pegylation of EPO change the pharmacological action of recombinant human EPO.[11]

> The pharmacological action of Ro 50-3821 is identical to that of erythropoietin beta in binding to surface receptors of erythroid progenitor cells to trigger proliferation, maturation, and terminal differentiation of colony-forming units.[12]

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subsequent pharmaceutical manufacturer may argue to the FDA that its product is as safe or as effective as another product already on the market, but it ought not be permitted to run from its earlier representation once the matter of patent infringement comes its way.").

[7] Separate Statement ¶ 23.

[8] Separate Statement ¶¶ 24-25.

[9] "Ro 50-3821/000 (PEG/EPO) is comprised of erythropoietin (EPO) with a linear methoxy-PEG molecule attached to it." Ex. 17 at ITC-R-BLA 00008462, BLA Report No. 1002576 August 17, 2001; *see also* Separate Statement ¶¶ 2, 21-22, 26-28.

[10] Ex. 4 at ITC-R-BLA-00004027; *see also* Separate Statement ¶¶ 27-28.

[11] Separate Statement ¶¶ 33-35, 38.

[12] Ex. 27 at ITC-R-IND-00062646; Separate Statement ¶ 38.

Peg-EPO can be used to treat anemia because it stimulates erythroid progenitor cells in the bone marrow to produce reticulocytes and red blood cells.[13] The erythropoietic activity of peg-EPO is indisputably due to the EPO protein contained in Mircera, not peg.[14]

The EPO in peg-EPO is produced by cells that Roche obtained from Genetics Institute – a company previously found to infringe Amgen's '008 patent.[15] The host cell line that Genetics Institute transformed with EPO DNA is identical to the host cell line that Lin used in Example 10 of his specification – both are cells from the ovary of a Chinese Hamster that are deficient in DHFR enzyme (and thus amenable to amplification).[16] Roche's EPO-producing cells (DN2-3α3 cells) contain an exogenous DNA sequence encoding the mature erythropoietin amino acid sequence of Figure 6 of Lin's patents spanning from positions +1 through +166.[17] That DNA sequence is amplified (*i.e.*, there are many copies of that DNA sequence in each cell) because the cells were selected for gene amplification using the DHFR amplified marker gene.[18] Glycosylated EPO is expressed from the cells into the culture medium.[19] The glycosylated EPO product is then purified from the culture medium.[20] The purified EPO product has the *in vivo* biological property of increasing production of reticulocytes and red blood cells.[21]

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[13] Separate Statement ¶¶ 7, 35-36.

[14] Separate Statement ¶¶ 31-32.

[15] *See* Ex. 10 at ITC-R-BLA-00005515.

[16] *Compare* Ex. 70, '933 Patent, Col. 25:46-51, *with* Ex. 9 at ITC-R-BLA-00004987.

[17] Separate Statement ¶ 8-11.

[18] Separate Statement ¶¶ 11-13.

[19] Separate Statement ¶¶ 14-16.

[20] Separate Statement ¶¶ 14-16.

[21] Separate Statement ¶ 7.

After purification of EPO, peg is attached by a single chemical reaction.[22] Peg-EPO is then formulated into the Mircera pharmaceutical composition, which is an aqueous solution containing peg-EPO that is packaged in vials or syringes.[23] Mircera is therapeutically effective when administered to patients with chronic kidney disease.[24]

III. ARGUMENT

As this Court has previously stated, "if there are no genuine issues of material fact, summary judgment is as appropriate in a patent infringement case as in any other."[25] Patent infringement is a two step inquiry: first, the court must construe the asserted claim; and second, the court must determine whether each limitation of the properly construed claim is present in the accused product or process.[26] Summary judgment on the issue of patent infringement is appropriate when no genuine issue of material fact precludes a finding that every limitation of the properly construed claim is found in the accused product or process.[27]

Here, Amgen seeks declaratory relief that if Roche engages in acts outside the safe harbor of 35 U.S.C. § 271(e)(1), such as the importation and sale of Mircera, it will directly infringe '422 Claim 1 and '933 Claim 3 under § 271(a) and '698 Claim 6 under § 271(g).

A. SUMMARY JUDGMENT OF INFRINGEMENT SHOULD BE DECLARED FOR '422 CLAIM 1 AND '933 CLAIM 3 PRODUCT CLAIMS UNDER § 271(A).

1. Mircera satisfies the claim limitations as construed by the Court.

Roche's sale of Mircera in the United States will literally infringe Amgen's '422 Claim 1

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[22] Separate Statement ¶¶ 21-22.

[23] Separate Statement ¶¶ 20, 23, 25.

[24] Separate Statement ¶ 37.

[25] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107 (D. Mass. 1998).

[26] *Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1356-57 (Fed. Cir. 2005).

[27] *Gart v. Logitech, Inc.*, 254 F.3d 1334, 1339 (Fed. Cir. 2001); *Bai v. L & L Wings, Inc.*, 160

and '933 Claim 3 because it meets every limitation as construed by the Court.[28]

With respect to '422 Claim 1,[29] there is no genuine dispute of fact that Mircera is a pharmaceutical composition or that it contains a pharmaceutically acceptable diluent (water for injection).[30] There also is no genuine dispute of fact that Mircera contains a "therapeutically effective amount" of peg-EPO or that the EPO starting material used to make peg-EPO was "purified from mammalian cells grown in culture."[31] The only real dispute between Amgen and Roche is whether Mircera comprises "human erythropoietin." The Court, however, has construed "human erythropoietin" to mean "A protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."[32] Since Roche has admitted to the FDA that the peg-EPO in Mircera has the "identical" amino acid sequence as epoetin beta (a recombinant human EPO), there is no genuine issue of material fact that this limitation is met.

F.3d 1350, 1353 (Fed. Cir. 1998).

[28] For the Court's convenience, Amgen has attached as Appendix A to the Statement of Undisputed Facts, a chart setting forth each claim, the Court's claim construction, and citations to the Separate Statement of Undisputed Facts establishing literal infringement of each element.

[29] '422 Claim 1 recites: "A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture."

[30] Separate Statement ¶¶ 23-25. Roche has previously argued '422 Claim 1 is limited to compositions with only one of a diluent, adjuvant, or carrier. Roche's argument, however, is contrary to the plain language of the claim as well as the specification. *See* Ex. 70, '933 Patent, Col. 33:52-55.

[31] Separate Statement ¶¶ 8-16, 36-37.

[32] Ex. 40, 4/17/07 *Markman* Tr. 27:8-10, 39:6-10.

A similar analysis applies with respect to '933 Claim 3.[33] There can be no genuine dispute that Roche does not obtain its EPO product (epoetin beta) from a natural source and it is, therefore, non-naturally occurring. Epoetin beta is the product of the expression in a mammalian host cell (CHO cells) of an exogenous DNA sequence encoding human EPO.[34] It is also undisputed that both epoetin beta and Mircera have the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells.[35] Since Mircera contains the non-naturally occurring EPO product claimed in '933 Claim 3, that claim will also be infringed.

2. Roche's addition of peg to the claimed EPO products does not avoid infringement.

Rather than raising a genuine issue of material fact, Roche's noninfringement defense rests on the false premise that the presence of peg in Roche's peg-EPO product precludes a finding of infringement. That premise fails because the presence of additional structure in an accused product does not avoid infringement.

The infringement inquiry requires the court to determine if each claim limitation is present in the accused product, not whether each feature or component of the accused product is present in the claim.[36] The presence of additional elements in the accused product that are not recited in the claims does not negate infringement.[37] The Federal Circuit has criticized non-

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[33] '933 Claim 3 recites: "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."

[34] Separate Statement ¶¶ 8-16.

[35] Separate Statement ¶¶ 7, 35.

[36] *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1482-84 (Fed. Cir. 1984); *see also Nazomi Communications, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1372 (Fed. Cir. 2005).

[37] *Amstar*, 730 F.2d at 1482 ("Modification by mere *addition* of elements of functions, whenever

infringement arguments that – like Roche's argument here – are based upon a feature of the accused apparatus missing from the claims:

> That view would stand the law of infringement on its head, and would fatally undermine the long-established legal principle that non-infringement is shown when an element or step in the claims is missing from the accused product or process, not vice versa.[38]

The first Federal Circuit decision to articulate this principle was *A.B. Dick Co. v. Burroughs Corp.*[39] In *A.B. Dick*, the claims recited a process for transferring ink to paper. The patented process was designed primarily for use in oscillograph machines, but, as the court noted, the claim did not limit the use of the process only in oscillographs. At issue was whether use of the defendant's dot matrix printer infringed the process claim.

The Federal Circuit reversed the district court's finding of non-infringement and rejected the defendant's argument that the claim for a method of writing was limited to use in oscillograph machines and could not read on methods of writing used in a dot matrix printer.[40] In doing so, the court succinctly stated the following principle:

> It is fundamental that one cannot avoid infringement merely by adding elements if each element recited in the claims is found in the accused device.[41]

The court illustrated the principle with the example of a claim to a pencil that is infringed when the pencil is incorporated into a complex machine:

> [A] pencil structurally infringing a patent claim would not become noninfringing when incorporated into a complex machine that limits or controls what the pencil can write. Neither would infringement be negated simply because the patentee

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made, cannot negate infringement without disregard of the long-established[] hornbook law . . . ").

[38] *Id.* at 1484.

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

[40] *Id.* at 703.

[41] *Id.* (citing *Temco Electric Motor Co. v. Apco Mfg. Co.*, 275 U.S. 319, 328 (1928)).

failed to contemplate use of the pencil in that environment.[42]

Because the claim for a method of writing reads on the writing mechanism in the defendant's dot matrix printer, the other features of the dot matrix printer were irrelevant to the infringement analysis.[43]

This Court and the Federal Circuit properly recognized that the presence of additional elements in the accused product does not negate infringement in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*[44] This Court found that Lin's '349 cell claims literally read on TKT's cells, and that the endogenous EPO promoter and regulatory elements in TKT's accused cells that were not recited in Lin's claims were irrelevant to TKT's infringement.[45] On appeal, the Federal Circuit affirmed this Court's finding that TKT's cells infringed Amgen's '349 claims.[46]

The rule that additional elements will not negate infringement applies unless the claim language explicitly excludes the presence of additional elements, or the inventor distinguished the claimed invention by reference to its exclusion of such structures.[47] However, Roche can

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[42] *Id.* at 703.

[43] *Id.*; *see also SunTiger, Inc. v. Scientific Research Funding Group*, 189 F.3d 1327, 1336 (Fed. Cir. 1999) ("The district court was persuaded that the gray coating on the BluBlocker lens changed an inherent property, thereby removing the accused lens from infringement. The district court's error lies in the fact that we have never required that a claim read on the entirety of an accused device in order to infringe. If a claim reads merely on a part of an accused device, that is enough for infringement. . . . Any other reasoning would allow an infringer to avoid infringement merely by adding additional elements to an infringing device.").

[44] *Amgen*, 126 F. Supp. 2d at 121-22; *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1351-52 (Fed. Cir. 2003).

[45] 126 F. Supp. 2d at 122 ("Thus, it matters not that the endogenous EPO promoter and enhancer sequences are present, as long as the cells contain the non-human (Claim 1) or other than human (Claim 4) EPO promoter sequences. Because the R223 cells do, they infringe Claims 1, 3, 4, and 6 of the '349 patent.").

[46] *Amgen*, 314 F.3d at 1351-52.

[47] This could occur by the use of "closed" transitional language, the use of language that by its nature excludes the presence of additional elements, or by a disclaimer of additional elements.

point to no language in '422 Claim 1 or '933 Claim 3 that excludes additional structure attached to the claimed human erythropoietin or glycoprotein products.[48] Thus, under the well-established principle that the presence of additional elements in an accused product does not avoid infringement, Roche's pegylation of Amgen's claimed products does not negate Roche's infringement.

3. Roche's peg-EPO is not so far changed in principle to avoid infringement via the "reverse doctrine of equivalents."

Roche has raised the "reverse doctrine of equivalents" as an equitable, affirmative defense. Roche bears the burden of making a *prima facie* showing that the accused device is outside the fair and equitable scope of the invention.[49] As described by the Supreme Court in *Graver Tank*, the reverse doctrine of equivalents may preclude literal infringement if "a device is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way, but nevertheless falls within the literal words of the claim . . . ."[50] The Federal Circuit has further described the doctrine as applying when, "despite the asserted claims literally reading on the accused device, 'it has been so changed that it is no longer the same invention.'"[51]

No Federal Circuit decision has ever affirmed a non-infringement decision based on the reverse doctrine of equivalents. As the Federal Circuit has noted, the defense is an

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None of these exceptions apply to Amgen's Asserted Product Claims. *See* Ex. 40, 4/17/07 *Markman* Tr. 79:7-80:13.

[48] *See* Ex. 40, 4/17/07 *Markman* Tr. 33:16-39:10.

[49] *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123-24 (Fed. Cir. 1985); *see generally Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 283-89 (D. Mass. 2004).

[50] *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S. 605, 608-09 (1950).

[51] *Amgen*, 314 F.3d at 1351 (quoting *Del Mar Avionics, Inc. v. Quinton Instr. Co.*, 836 F.2d 1320, 1325 (Fed. Cir. 1987)).

"anachronistic exception,"[52] and for good reason. After *Graver Tank*, Congress enacted 35 U.S.C. § 112, which imposes explicit requirements for written description, enablement, and definiteness that severely limit the need for and reach of the reverse doctrine of equivalents defense.[53] Here, Amgen's patents have withstood intense attacks under § 112.

Roche's reverse doctrine of equivalents allegations should not preclude a summary adjudication in this case. Roche cannot make a *prima facie* showing and no reasonable trier of fact could find that Roche's peg-EPO performs its function in a substantially different way from the claimed EPO products. To the contrary, peg-EPO stimulates the formation of erythroid progenitor cells into red blood cells in the same way by activating the same EPO receptors to initiate the same signaling pathway in the body.[54] Nor may Roche rely on the presence of unclaimed additional structures like peg to avoid infringement under the reverse doctrine of equivalents if all of the claimed limitations are satisfied.[55]

Even if Roche's pegylation of Lin's claimed EPO products constituted an "improvement" of those products – which it does not – over a century of case law has firmly established that an accused infringer, even an innovator, cannot appropriate the claimed invention of another simply because he has improved upon it.[56] Recognizing this fundamental principle, the Supreme Court

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[52] *Tate Access Floors, Inc. v. Interface Architectural Res., Inc.*, 279 F.3d 1357, 1368 (Fed. Cir. 2002).

[53] *Id.* at 1368.

[54] Separate Statement ¶¶ 33-34.

[55] *See Seiko Epson Corp. v. Print-Rite Holdings, Ltd.*, 2005 U.S. Dist. LEXIS 43200 at *26 (D. Or. Mar. 5, 2005) (rejecting reverse doctrine of equivalents defense on summary judgment); *see also N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 944-45 (Fed. Cir. 1990).

[56] *See Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318, 1324 (Fed. Cir. 2000); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1580 (Fed. Cir. 1984) ("[W]here defendant has appropriated the material features of the patent in suit, infringement will be found 'even when those features have been supplemented and modified to such an extent that the defendant may be

has stated, "It is well established that an improver can not appropriate the basic patent of another, and that the improver without a license is an infringer, and may be sued as such."[57] So even if Roche's pegylation of EPO were an "improvement," Roche would nevertheless be liable for infringement because it has appropriated Lin's underlying invention.

B. SUMMARY JUDGMENT OF INFRINGEMENT SHOULD BE DECLARED FOR LIN'S '698 CLAIM 6 PROCESS CLAIM UNDER § 271(G).

As described above, there is no genuine issue of material fact that Roche uses Amgen's patented process in Germany and that the EPO in peg-EPO is the product of Amgen's patented process.[58] '698 claim 6 requires:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

Roche grows vertebrate cells (CHO cells) under suitable nutrients conditions to make its EPO product (epoetin beta). The cells contain amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6.[59] The glycosylated EPO polypeptide expressed from the cells is then isolated (separated away from) the cells and the growth medium, and it has the recited *in vivo* biological activity.[60]

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entitled to a patent for the improvement.'"); *Tilghman v. Proctor*, 102 U.S. 707, 732 (1880) ("[T]he introduction of an improvement gives no title to use the primary invention upon which the improvement is based.").

[57] *Temco*, 275 U.S. at 328.

[58] *See supra* Part II; Separate Statement ¶¶ 8-16 and Appendix A.

[59] Separate Statement ¶ 11, 13.

[60] Separate Statement ¶ 7, 14-16; Ex. 40, *Markman* Hearing Tr. at 97:20-98:5.

The only remaining inquiry under § 271(g) is whether Roche's importation of peg-EPO nevertheless avoids infringement because the glycosylated EPO has been (a) "materially changed by subsequent processes" or (b) is a "trivial and non-essential component of another product."

The two-part test in § 271(g) focuses on the differences, if any, between the EPO of the claimed process and the EPO in peg-EPO, not differences between the product of the claimed process and the imported product. The statutory language makes this clear. First, the statute asks whether the product of the process – not the imported product – has been materially changed by subsequent processes prior to importation. Alternatively, the statute asks whether the product of the process has become merely a trivial and nonessential component of the imported product. If, as Roche contends, the relevant legal inquiry were to compare the product of the process (EPO) with the totality of the imported product (peg-EPO), the second statutory test would be superfluous. If that were the relevant legal analysis, then a "material change" would occur every time a product of a claimed process was incorporated into another product, and there would be no purpose served by inquiring whether the incorporated product had become a "trivial and non-essential component" of the imported product. But that is not the law.

The recent decision in *Oki America, Inc. v. Advanced Micro Devices, Inc.*[61] is instructive. In that case, the patent claim at issue related to a process for making a semiconductor wafer with smooth edges. As a result, the semiconductor wafers had less debris leading to less defects in the semiconductor chips that were diced from the wafers. Moving for summary judgment of noninfringement, the defendant conceded it used the claimed process outside the United States. However, it argued that it materially changed the product of the process (semiconductor

[61] No. C-04-03171, 2006 WL 2711555 (N.D. Cal. Sept. 21, 2006).

devices from a wafer substrate lacking certain debris) by performing subsequent processing steps. The court, however, rejected the argument:

> Oki also argues that the numerous other wafer processing steps (mask placement, photolithography, resist development and removal, dicing, encapsulation) required for fabrication would anyway constitute a material change. As stated above, however, ***the product is a device lacking certain debris, and this aspect of the product remains unchanged by any subsequent processing***. . . . The ***subsequent processing steps***, such as photolithography, resist development and removal, dicing, and encapsulation, ***do of course make material changes to the physical and electrical properties of the semiconductor substrate, but these changes do not impact the product of Allen process, a debris-free device***.[62]

Here, prior to importation, Roche makes EPO using Lin's claimed processes and then pegylates the EPO, by attaching a peg chain to the EPO polypeptide. The peg chain forms a single amide bond at either the N-terminal alanine or the side chain of an internal lysine.[63] This reaction does not alter the amino acid sequence or the carbohydrate composition of the glycoprotein.[64] In fact, in efforts to gain FDA approval, Roche told the FDA the EPO in peg-EPO is "identical" to the EPO that is used as a starting material in the pegylation process. Thus, like the debris-free wafer in *Oki*, the EPO product of the process is not "changed" as a result of subsequent processing.

Roche's own depictions of the three-dimensional structure of EPO and peg-EPO further illustrate that EPO is not materially changed by Roche's pegylation process. In the figure below, the EPO in peg-EPO (CERA) is shown to be the identical size and shape before and after the attachment of peg during pegylation:[65]

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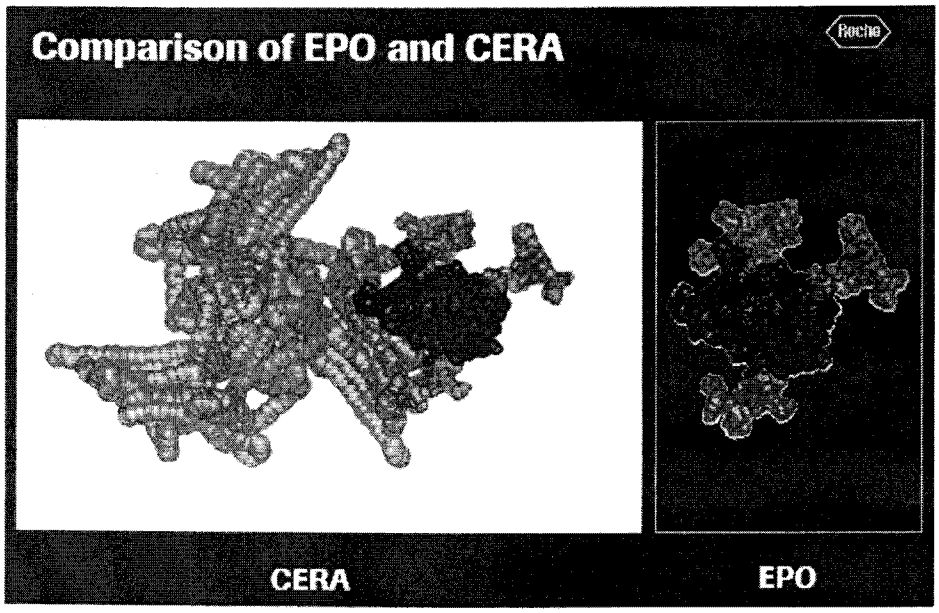
[62] *Id.* at *14 (emphasis added).

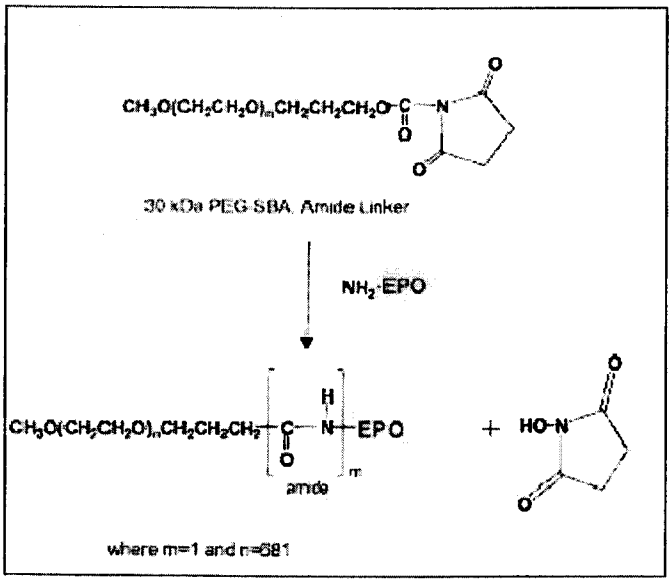
[63] Separate Statement ¶¶ 21-22.

[64] Separate Statement ¶¶ 27-28.

[65] Ex. 31 at AM44 0038918.



Similarly, when Roche scientists described the chemical structure of peg-EPO, they described the EPO starting material as being present after the pegylation reaction.[66]



A chemical bond between EPO and peg is irrelevant to infringement of Lin's process claims. The glycosylated EPO of the claims has been construed to include the 165 amino acid sequence of human EPO with attached carbohydrates. The addition of the chemical bond to EPO

does not change its amino acid sequence or cause it to cease being EPO under the Court's construction. The imported peg-EPO product contains the EPO product of Lin's patented processes; it is not changed in any way that takes it outside the scope of Lin's claims. Thus, no genuine factual issues preclude a finding that Roche's importation of peg-EPO will infringe '698 Patent, Claim 6.

Even if the addition of a single chemical bond were legally relevant, the issue becomes whether such change is "material." In light of the legislative history of § 271(g) and Federal Circuit authority, the EPO in peg-EPO is not "materially changed" by pegylation as a matter of law.

In *Eli Lilly & Co. v. American Cyanamid*, the Federal Circuit stated, "In the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties."[67] At issue were claims to a method of making a precursor to the antibiotic cefaclor. Four subsequent process steps were necessary to convert the precursor into cefaclor, the product that was imported into the United States. These steps physically altered the structure of the precursor molecule: a hydroxy group was removed and replaced with a chlorine atom, a phenylacetyl group was removed and replaced with a phenylglycyl group, and a para-nitrobenzyl carboxylate ester group was removed.[68] The only commonality between the precursor of the claimed process and the imported product was the cepham nucleus, which is common to thousands of compounds.[69] Each of the substitutions made to the structure of the precursor also changed the function of the precursor, transforming it

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[66] Ex. 43 at R000081258.

[67] 82 F.3d 1568, 1573 (Fed. Cir. 1996). The Federal Circuit has employed several different tests, while noting that none are conclusive. *Id.* at 1578.

[68] *Id.* at 1570.

from an ineffective antibiotic into an orally effective antibiotic: the carboxyl group was important for antibacterial activity; the chlorine atom increased the antibiotic potency; and the phenylglycyl group enabled the imported cefaclor to be effective when taken orally.[70] Before those changes, the ***precursor itself had no utility*** as an antibiotic.[71] Under these facts, the court held that "a change in the chemical structure and properties as significant as the change between compound 6 and cefaclor cannot lightly be dismissed as immaterial."[72]

In contrast to the facts of *Lilly*, Roche's pegylation of EPO does not modify the structure or utility of EPO. Aside from the displacement of a single hydrogen atom (which does not change the amino acid sequence), the pegylation process is purely additive, and EPO's structure is otherwise unaffected: the amino acid sequence and carbohydrate composition of the imported peg-EPO product is identical to that of the EPO starting material.[73] Additionally, the only claimed property of EPO (*i.e.*, the *in vivo* biological property of causing bone marrow cells to increase the production of reticulocytes and red blood cells) is unchanged by pegylation.[74]

The *Lilly* court identified chemical modifications that are only "trivial or conventional in nature" such as "modifications which result in the formation of simple derivatives" that would not constitute a material change. [75] Pegylation of proteins is indisputably a conventional process

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[69] *Id.* at 1573.

[70] *Id.* at 1570.

[71] *Id.* at 1577.

[72] *Id.* at 1573.

[73] Separate Statement ¶¶ 21-22, 26-28.

[74] Separate Statement ¶¶ 7, 37.

[75] *Lilly*, 82 F.3d at 1575 (quoting H.R.Rep. No. 807, 99th Cong., 2d Sess. at 21-22 (1986)).

used to form derivatives of biologically active molecules.[76] For example, Roche told the FDA in 2001:

> "In order to circumvent the short half-lives of recombinant proteins and to enhance the pharmacokinetic and pharmacodynamic properties that result in sustained clinical response, it is now ***common practice*** to chemically conjugate protein therapeutics such as EPO to water soluble polymers, like polyethylene glycol (PEG). . . ."[77]

Moreover, the fact that Roche selected its pegylation process from commercially available processes, and that the pegylation reaction is a simple one-step reaction, and that all of the pegylation chemistries tested in its feasibility study had biological activity, speaks to the conventional nature of pegylation.[78] Thus, these undisputed facts further support a conclusion that the EPO in peg-EPO is not materially changed because pegylation is a conventional process.

Lastly, EPO is indisputably not a "trivial and non-essential component" of peg-EPO. As described above, PEG is inert, cannot bind to EPO receptors, and cannot stimulate erythropoiesis.[79] EPO is, in fact, the essential component of peg-EPO, as it is entirely responsible for its therapeutic utility.

IV. CONCLUSION

For the foregoing reasons, summary judgment of infringement should be entered against Roche with respect to '422 Claim 1, '933 Claim 3, and '698 Claim 6.

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[76] Separate Statement ¶¶ 39-41. The *Oxford Dictionary of Biochemistry and Molecular Biology* (Anthony D. Smith et al. eds., rev. ed. 1997) defines a "derivative" as "any compound that may, at least theoretically, be formed from another compound to which it is structurally related."

[77] Ex. 24 at ITC-R-IND-00000822.

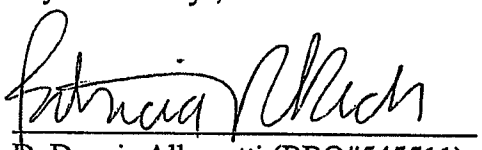
[78] Separate Statement ¶¶ 21-22; Ex. 53, 4/06/07 Expert Report of Vladimir P. Torchilin, Ph.D., D.Sc., at ¶¶ 92-93.

[79] Separate Statement ¶¶ 31-32.

Dated: June 14, 2007

Respectfully Submitted,

AMGEN INC.,
By its attorneys,



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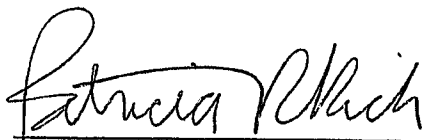

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