Exhibit A

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF MASSACHUSETTS**

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| AMGEN, INC.,<br><br>Plaintiff,<br><br>v.<br><br>F. HOFFMANN-LA ROCHE, LTD, ROCHE DIAGNOSTICS GmbH, HOFFMANN-LA ROCHE INC.,<br><br>Defendants. | Civil Action No. 05-12237 WGY<br><br>U.S. District Judge Young |

**ROCHE'S MOTION FOR JUDGMENT OF NON-INFRINGEMENT AS A MATTER OF LAW**

*Roche will file a supplemental memorandum with a more complete recitation of its arguments and relevant evidence on or before October 16th*

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## Cases

**Rules**

## I. INTRODUCTION

Defendants F. Hoffmann-La Roche, Ltd, Roche Diagnostics GmbH and Hoffmann-La Roche Inc. ("Roche") submit this memorandum of law in support of their motion for judgment as a matter of law, pursuant to Fed. R. Civ. P. 50, that Roche does not infringe the asserted claims of the patents-in-suit. Roche's motion should be granted in all respects because, given the evidentiary record in this case:

- A reasonable jury could not conclude that Amgen has met its burden of proving that Roche's imported MIRCERA® product literally infringes claim 7 of the '349 patent because Amgen has put forward no evidence that Roche uses vertebrate cells capable of producing a certain number of "U of erythropoietin" as determined by radioimmunoassay, the test specified in the claim. In addition, CERA™, the active ingredient, is not made in a vertebrate cell, and has a different amino acid sequence than any product of '349 claim 7. No reasonable jury could conclude that Amgen has met its burden of proving that MIRCERA is not "materially changed" from the product of '349 claim 7. Finally, there is no legally-recognized basis for infringement under 35 U.S.C. § 271(g) for importing the product of a process performed outside the United States where the process satisfies the elements of a process claim only under the doctrine of equivalents.
- A reasonable jury could not conclude that Amgen has met its burden of proving that Roche's imported MIRCERA product literally infringes the process claims of the '868 patent because MIRCERA (or CERA) is not made in a mammalian cell, CERA has a different amino acid sequence than the product of the '868 claims, CERA is not made by transforming or transfecting a cell with an isolated DNA sequence and the isolated product of Amgen's '868 claims contains impurities not present in CERA, rendering the *in vivo* activity of the isolated product uncertain. Moreover, a reasonable jury could not determine that Amgen has met its burden of proving that MIRCERA is not materially changed from the product of the '868 process claims. Finally, there is no legally-recognized basis for infringement under 35 U.S.C. § 271(g) for importing the product of a process performed outside the United States where the process satisfies the elements of a process claim only under the doctrine of equivalents.
- A reasonable jury could not conclude that Amgen has met its burden of proving that Roche's imported MIRCERA product literally infringes the process claims of the '698 patent because MIRCERA (or CERA) is not made in a vertebrate cell, CERA has a different amino acid sequence than the product of the '698 claims and the isolated product of Amgen's '698 claims contains impurities not present in CERA, rendering the *in vivo* activity of the isolated product uncertain. Moreover, a reasonable jury could not determine that Amgen has met its burden of proving that MIRCERA is not materially changed from the product of the '698 process claims. Finally, there is no legally-recognized basis for infringement under 35 U.S.C. § 271(g) for importing the product of a process performed outside the United States where the process satisfies the elements of a process claim only under the doctrine of equivalents.

- A reasonable jury could not conclude that Amgen has met its burden of proving that Roche's MIRCERA product literally infringes the claims of the '933 patent because CERA is "one molecule" with an amino acid sequence that is different than the amino acid sequence of the product of the '933 claims, the epoetin beta starting material has not been shown to be "non-naturally occurring," as required by the claims, and CERA is not made in mammalian cells.
- Amgen cannot prevail on infringement of the '933 patent under the doctrine of equivalents because Amgen is estopped from arguing the doctrine of equivalents and, in any event, Amgen has failed as a matter of law to present evidence on an element-by-element basis to support its claims of equivalence as required.

## II. JUDGMENT AS A MATTER OF LAW

"[A] motion for judgment as a matter of law may be made at any time before the case is submitted to the jury." Fed. R. Civ. P. 50(a)(2). Judgment as a matter of law is appropriate when "'there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue.'" *TI Group Automotive Sys., Inc. v. VDO N. Am., L.L.C.*, 375 F.3d 1126, 1133 (Fed. Cir. 2004), quoting Fed. R. Civ. P. 50(a)(1). Amgen's evidence of infringement would not permit a reasonable jury to conclude that Amgen has proved that Roche infringes any of the asserted claims of the patents-in-suit.

## III. NO REASONABLE JURY COULD FIND THAT ROCHE'S MIRCERA PRODUCT INFRINGES THE ASSERTED CLAIMS OF THE PATENTS-IN-SUIT[1]

### A. Legal Standard

As the patentee, Amgen has the "burden of proving infringement by a preponderance of the evidence." *Centricut, LLC v. Esab Group, Inc.*, 390 F.3d 1361, 1367 (Fed. Cir. 2004). "If the accused product meets each of the limitations contained in a claim" as properly construed, "then the product literally infringes that claim. If, however, even one limitation is not met, then the product

[1] Roche limits its discussion in this memorandum to the more glaring omissions and failures in Amgen's affirmative infringement case. The absence of discussion on particular claim elements should not be construed as an admission by Roche that it's MIRCERA product infringes those particular claim elements. Similarly, the absence of discussion on particular infringement-related issues should not be construed as a concession by Roche to Amgen's position.

does not literally infringe." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 117 (D. Mass. 2001).

### B. No Reasonable Jury Could Conclude That MIRCERA Infringes The Asserted Process Claims

As Amgen recognizes, Roche cannot infringe claim 7 of the '349 patent, claims 1-2 of the '868 patent and claims 6-9 of the '698 patent under 35 U.S.C. § 271(a) because Roche does not practice these claimed processes in the United States. At best, Amgen could show that Roche practices the processes of these claims outside of the United States and infringe under § 271(g) by importing the product of said processes. Moreover, even if Amgen could prove that Roche's manufacturing activities outside of the U.S. satisfy the process claims -- which it cannot -- Amgen also has the burden of establishing that the product ultimately imported by Roche product is not materially changed from the product of the processes claimed in '349 claim 7, '868 claims 1-2 and '698 claims 6-9. Amgen has not met its burdens.

#### 1. Amgen Has Not Proven That Roche Infringes '349 Claim 7

##### a. Amgen Has Not Proven That Roche Practices The Process Of '349 Claim 7

Claim 7 of the '349 patent requires the use of cells which have the capacity to produce specified number of "U of erythropoietin ... as determined by radioimmunoassay."[2] However, Roche does not employ radioimmunoassay ("RIA") in its production process, (Lodish 2444:13-15, 2503:5-9, 2504:9-10), nor did Amgen present RIA data as to the production capability of the cells used in making Roche's reaction material. Amgen's expert Dr. Lodish did no more than perform a

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[2] Claim 7 of the '349 patent reads: "A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5**,** or 6." Claim 1, from which claim 7 depends, reads: "Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin." (TRX 4).

calculation based on data reported in Roche's BLA which was not generated by RIA. Dr. Lodish reasoned as follows: (1) Roche's BLA states that, as measured by ELISA, the cells Roche uses produce 7.4 micrograms of EPO per million cells for 48 hours; (2) Roche's BLA defines the specific activity of EPO as 207,700 units per milligram; (3) using the specific activity one can convert the 7.4 micrograms of EPO to 1,500 units of EPO per million cells in 48 hours; and (4) one would expect ELISA results (per the BLA) and RIA (per the claim) to be the same. Thus, Dr. Lodish concluded that Roche's cells exceed claim 1's production capability of "100 U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay." (*See* Lodish 2444:19-2448:16, 2449:23-2450:4).

Plainly, however, there are fatal gaps in Dr. Lodish's analysis. The BLA's reference to 7.4 micrograms of EPO per million cells in 48 hours was measured *in vitro* by ELISA. Yet, the specific activity reported in the BLA for EPO was measured *in vivo* in a mouse bioassay following a complex purification procedure. (TRX 52 at ITC-R-BLA-00005581). Thus, Dr. Lodish's calculation mixed apples and oranges. Dr. Lodish offered no support or explanation for his conversion method. He did not even assert that *in vitro* assays of human EPO and *in vivo* mouse assays of human EPO are interchangeable.

Having thus supposedly arrived at an EPO production level as measured by ELISA, Dr. Lodish asserted that even though the claims specifically prescribe an activity level as determined by RIA, one can simply assume that the activity level as measured by Roche's ELISA would have been the same if measured by RIA as required by the claim. (Lodish 2451:3, 2452:11-15). Again, Dr. Lodish offered no documentary support to corroborate this assumption. The only "evidence" even purported to establish a correlation were experiments discussed in expert reports of two other Amgen experts, Drs. Kolodner and McLawhon. (*See* Lodish 2452:19-2455:11). However, neither the conditions under which these experiments were performed nor are the actual of these

experiments is in evidence, nor could they be. Dr. McLawhon testified that he did not personally run any experiments and was not ever in Chicago when the tests were allegedly performed. (McLawhon 5/17/07 Depo. Tr., 95:1-11).

Moreover, as Amgen's counsel admitted, Dr. Lodish's calculations were based on reported measurements of the purified material, ***not*** the material being secreted by the cells into the medium of their growth, as required by claim 7. (Trial Tr. 2449:6-7); *see also Levinsky's, Inc. v. Wal-Mart Stores, Inc.*, 127 F.3d 122, 134 (1st Cir. 1997) ("Certainly, an admission of counsel during trial is binding on the client"). Furthermore, the values Dr. Lodish used to make his calculation were overstated because these cells had multiple periods of methotrexate treatment according to a method not normally used by Roche in production of its starting material. (TRX 52 at ITC-R-BLA-00005073-74). Dr. Lodish's calculation was also based on cells that were lysed (or busted open) whereas claim 7 requires a measurement based solely on what is secreted into the cell medium, which would be significantly less than the amount of EPO from a lysed cell. Nor do the figures in the BLA relied upon by Dr. Lodish account for the actual production rates of epoetin beta used as a starting reagent in the synthesis of CERA. Rather, the BLA data relied upon by Dr. Lodish reports results from cells that had already undergone a full production cycle over several weeks, and one cannot correlate the output of these cells with cells Roche actually employs during its manufacturing process. (*See* TRX 52 at ITC-R-BLA-00005073-74).

Accordingly, not only was Dr. Lodish's testimony highly misleading and prejudicial, it was also wholly irrelevant. With nothing to go by other than the conclusory and unsubstantiated opinions of Dr. Lodish, which are manifestly flawed, no reasonable jury could conclude that Roche practices the process of '349 claim 7. *See Richmond Steel Inc. v. Puerto Rican Am. Ins. Co.*, 954 F.2d 19, 22 (1st Cir. 1992) (to withstand a motion for directed verdict, "plaintiff may not rely on conjecture or speculation"); *Yoon Ja Kim v. Conagra Foods, Inc.*, 465 F.3d 1312, 1320 (Fed. Cir.

2006) (expert's conclusory testimony insufficient to withstand judgment as a matter of law).

Finally, Dr. Lodish testified Roche's production DNA plasmid includes a promoter of non-human origin. (*See* Lodish 2408:16-25). Independent claims 1-6 of the '349 patent require vertebrate cells comprising DNA sequences which control transcription of DNA for production of human erythropoietin. Dr. Lodish offered no evidence to suggest that the promoter present in Roche's plasmid exerts such control.

**b. Amgen Has Not Proven That Roche's Imported MIRCERA Product Is Not Materially Changed From The Product Of The Claimed Process**

Even if a reasonable jury could conclude that Roche practices the process of '349 claim 7, Amgen has not proven that Roche's imported product, MIRCERA, is not materially changed from the product of that process. In *Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568 (Fed. Cir. 1996), the Federal Circuit stated that § 271(g) "permits the importation of an item that is derived from a product made by a patented process as long as that product is 'materially changed' in the course of its conversion into the imported item." *Id*. at 1572. The issue under § 271(g) is "the substantiality of the change between the product of the patented process and the product that is being imported." *Id*. at 1573. "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." *Id*. The patentee "bears the burden of proof on the issue of material change" under § 271(g). *Genentech, Inc. v. Boehringer Mannheim GmbH*, 47 F. Supp. 2d 91, 108 (D. Mass. 1999).

Amgen does not -- and cannot -- contend that the process in '349 claim 7 includes any purification step. Accordingly, the product of the process claimed in '349 claim 7 is a crude isolate containing human erythropoietin in addition to other materials that are not "human erythropoietin" according to the Court's construction. Roche materially changes the crude isolate recovered from cells by performing a series of patented purification steps to remove potentially harmful chemicals.

In other words, the purification steps remove portions of the product of the asserted process claims. While EPO produced by a single vertebrate or mammalian cell can consist of a heterogeneous mixture of different isoforms having from zero to fourteen sialic acid residues and, as a result, different electrical charges, Roche's purification method materially changes the recovered product by selecting out predominantly six isoforms. The only "evidence" Amgen offered in response to these facts is Dr. Lodish's unsupported testimony that "recombinant human EPO is unchanged by removing impurities." (Lodish 2486:24-25). His testimony is plainly contradicted by Amgen's other witnesses, Drs. Varki and Strickland, who admitted that purification techniques -- which are not required by the asserted claims -- do change the structural and chemical properties of human EPO produced with techniques based on recombinant DNA. (Varki 2250:9-25; Strickland 2157:12-2158:13; TRX 2105).

In any event, Roche makes a further, more drastic, material change by chemically and irreversibly reacting purified epoetin beta with an activated polyethylene glycol molecule to create CERA. CERA differs from the epoetin beta starting material in terms of structure and function, including differences in pharmacodynamic and pharmacokinetic properties. It is undisputed that CERA has approximately 5,000 more atoms, a significantly higher molecular weight, a longer half-life and a lower binding affinity than EPO, among other material distinctions. This Court has pointed to the same kinds of differences between the imported product and the product of the patented process in finding material change under § 271(g). *See Genentech*, 47 F. Supp. 2d at 112. Dr. Lodish attempted to minimize the materiality of these admitted differences, stating that the pegylation reaction does not change the three-dimensional structure of EPO or its biological function. (Lodish 2487:5-2488:1). However, Dr. Lodish applied the wrong analysis under §271(g). As Dr. Lodish admitted, CERA is "one molecule," not separate PEG and EPO molecules. (Lodish 2515:14-19). Accordingly, the appropriate inquiry is not whether the "EPO portion" of CERA is

different from the EPO product covered by Amgen's process claims. Rather, the question is whether MIRCERA imported by Roche is materially changed ***from the EPO product of the processes of Amgen's claims.***

Material change is further evidenced by the fact that when Roche carries out its synthetic process for MIRCERA, the amino acid sequence of the epoetin beta reaction material is chemically modified. Amgen does not claim that "erythropoietin" in claim 7 means anything other than "human erythropoietin," which the Court has defined as "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." (D.I. 613 at 15).[3] Dr. Lodish admitted, however, that the amino acid sequence contained in Roche's MIRCERA product is not the same as the "amino acid sequence of EPO isolated from urine." While he estimated that the amino acid sequence of MIRCERA is "99.75 percent identical" to the amino acid sequence of EPO isolated from urine, that is not the 100% that is required for a finding of literal infringement. (Lodish 2510:7-2514:7). Indeed, the chemical reaction employed in creating CERA replaces the hydrogen on the lysine amino acid with a carbon atom. (Lodish 2512:2-13). In his textbook, Dr. Lodish admitted that chemically modified amino acids constitute "different amino acids." (Lodish 2522:7-16).

Dr. Lodish also testified that because MIRCERA binds to the EPO receptor, it must be the same as Amgen's claimed recombinant EPO. He referred to this by a "key-into-lock" analogy. (Lodish 2490:25-2491:13). However, Dr. Lodish admitted on cross-examination that "the mere fact that something binds to the EPO receptor doesn't tell you that it's EPO." (Lodish 2524:10-12). Indeed, Aranesp, which is not covered by the patents-in-suit, has a different amino acid sequence

[3] Although the Court's construction for "human erythropoietin" is directed to claim 1 of the '422 patent in the Markman Memorandum and Order, Amgen's Markman briefing indicated that its proposed construction for "human erythropoietin" applies to claim 7 of the '349 patent. (D.I. 323 at 5).

than Amgen's recombinant EPO, yet still binds to the EPO receptor and triggers red cell production. (Lodish 2525:2-10).

In sum, Roche's production process results in a product (MIRCERA) that is materially changed from the claimed process. Roche's imported product, following numerous material changes, is not produced in a vertebrate cell, (Lodish 2505:12-18, 2506:7-14, 2507:17-20, 2508:22-23), is not recovered from cell culture, (Lodish 2506:15-18), and is no longer "erythropoietin" as defined by the Court. (Lodish 2510:7-2514:7, 2512:2-13, 2522:7-16). Moreover, MIRCERA has a higher molecular weight, a lower binding affinity, a quicker cell metabolism, a substantially longer half-life, a substantially longer potency and different intracellular signaling properties. Accordingly, no reasonable jury could conclude that Roche infringes '349 claim 7.

**2. Amgen Has Not Proven That Roche Infringes The Asserted Claims Of The '868 Patent**

**a. Amgen Has Not Proven That Roche Practices The Processes Of The Asserted Claims Of The '868 Patent**

No reasonable jury could conclude that Amgen has met its burden of proving that in manufacturing MIRCERA outside of the U.S., Roche practices the asserted claims of the '868 patent.[4] Amgen has not shown that Roche uses "cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin." At the time of Lin's application, DNA-mediated gene transfer techniques, such as calcium phosphate precipitation, electroporation and microinjection, were available for transferring isolated and purified DNA fragments into host cells. The specification of the Amgen patents discloses several examples of host cell transformation and

[4] Claim 1 of the '868 patent reads: "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, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and (b) isolating said glycosylated erythropoietin polypeptide therefrom." Claim 2 further refines claim 1 by limiting the "mammalian host cells" to CHO cells. (TRX 2).

transfection with an isolated DNA sequence, including introduction of purified and isolated DNA into COS cells (TRX 1, Examples 6 and 7), CHO cells (TRX 1, Example 8) and *E. Coli* (TRX 1, Example 12) via DNA mediated gene transfer. However, Amgen submitted no evidence that the protoplast fusion method used to create Roche's production cell bank, in which cells are "smushed" together, involves the transfer of *isolated* DNA. Dr. Lodish offered no more than conclusory statements -- without support -- that did not address the protoplast fusion method that Roche employs. (Lodish 2414:6-2416:23). Simply stated, Roche's cells are not transformed or transfected with an isolated DNA sequence, as required by the claims, and Amgen has not submitted evidence that would allow a reasonable jury to conclude otherwise.

Amgen has submitted no evidence that the crude isolate from Roche's cells has the *in vivo* biological activity required by the claims. The concluding step of the processes of the claims of the '868 patent is "isolating said glycosylated erythropoietin polypeptide" from the cells which produce the protein. In securing its patents in the PTO, Amgen asserted that the term "isolating" means "nothing more than separating the expressed product from the cell," flatly denying that the step of "isolating" includes "purification." (TRX GUK Interf. No. 102,097, Brief for the Senior Party Lin at 48, 58).[5] At the Markman hearing in this case, the Court acknowledged the binding effect of Amgen's statements and held that the term "isolating said glycosylated erythropoietin polypeptide" means separating said glycosylated erythropoietin polypeptide. (Markman Hearing Tr. 97:20-98:5). Hence, as noted above, the final product of the process recited in the claims, which ends with isolation, is the "crude isolate" -- the unpurified expression product that is "isolated" from the cells.

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[5] TRX GUK was admitted into evidence during the hearing on obviousness-type double patenting. (October 1, 2007 Hearing Tr. 46:9-17). Even if not considered as "evidence" in the infringement portion of these proceedings, Roche respectfully requests that the Court take judicial notice of Amgen's position in construing this claim limitation, which is a question of law.

However, Amgen has presented no evidence at all that Roche's crude unpurified isolate has "the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Accordingly, no reasonable jury could find that Amgen has proved that Roche infringes claims 1 and 2 of the '868 patent.

**b. Amgen Has Not Proven That Roche's Imported MIRCERA Product Is Not Materially Changed From The Product Of The Claimed Process**

Even if a reasonable jury could conclude that Roche practices the processes claimed in '868 claims 1 and 2, Amgen has not proven that Roche's imported MIRCERA product is not materially changed from the product of Amgen's claimed processes. As explained above with regard to '349 claim 7, the evidence is crystal clear that MIRCERA results from multiple material changes: (1) Roche purifies the crude isolate to transform a therapeutically useless material into a therapeutically useful drug product; (2) CERA has a different amino acid sequence than product of Amgen's claimed processes; (3) Roche chemically synthesizes epoetin beta and PEG to form "one molecule" with different pharmacokinetic and pharmacodynamic properties; and (4) Roche's imported product is not capable of being produced in a mammalian cell, among other changes.

**3. Amgen Has Not Proven That Roche Infringes The Asserted Claims Of The '698 Patent**

**a. Amgen Has Not Proven That In Manufacturing MIRCERA Outside Of The United States Roche Satisfies The Elements Of The Asserted Claims Of The '698 Patent**

Amgen has not presented sufficient evidence for a reasonable jury to conclude that Roche practices any of the asserted claims of the '698 patent.[6] As in the case of the '868 patent, the

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[6] Claim 6 of the '698 patent reads: "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

(continued...)

product of the claimed process in the '698 patent is the crude isolate -- the product of the process which concludes with "isolating said glycosylated erythropoietin polypeptide" expressed by said cells -- not purified epoetin beta. The Court has ruled that "expressed" means produced by a cell and recovered from a cell. (D.I. 613 at 32 n.3). However, there is no evidence that Roche's crude isolate has the claimed "*in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."

**b. Amgen Has Not Proven That Roche's Imported MIRCERA Product Is Not Materially Changed From The Product Of The Claimed Process**

Even if a reasonable jury could conclude that Roche practices the processes of the asserted '698 claims, Amgen has not proven that Roche's imported MIRCERA product is not materially changed from the product of Amgen's claimed processes. As explained above, the evidence clearly shows that MIRCERA results from multiple material changes: (1) Roche purifies the crude isolate to transform a therapeutically useless material into a therapeutically useful drug product; (2) MIRCERA has a different amino acid sequence than product of Amgen's claimed processes; and (3) Roche chemically synthesizes epoetin beta and mPEG-SBA to form "one molecule" with different pharmacokinetic and pharmacodynamic properties; and (4) Roche's imported product is not capable of being produced in a mammalian cell, among other changes.

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DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells." Claims 7 through 9 further refine claim 6 by adding limitations to "wherein said vertebrate cells further comprise amplified marker gene DNA," "wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA," and "wherein said cells are mammalian cells," respectively.

### C. No Reasonable Jury Could Conclude That MIRCERA Infringes The Asserted Claims Of The '933 Patent[7]

Amgen has presented wholly insufficient evidence for a reasonable jury to conclude that Roche infringes the asserted claims of the '933 patent, either literally or under the doctrine of equivalents.[8]

#### 1. No Reasonable Jury Could Conclude That MIRCERA Literally Infringes The Asserted Claims Of The '933 Patent

##### a. Amgen Has Not Proven That Roche Infringes Claims 3, 7 Or 8 Of The '933 Patent

As explained above, it is undisputed that Roche's "glycoprotein product," CERA, is not "a product of ... expression in a mammalian host cell." CERA is not and cannot be produced by living cells and is substantially different in structure and function from a product of the recited process. Rather, CERA is a chemically synthesized compound that is created in the laboratory. Dr. Lodish repeatedly admitted as much. (Lodish 2505:12-18, 2506:7-14, 2507:17-20, 2508:22-23). CERA is distinct from the epoetin beta and mPEG-SBA starting materials and CERA cannot be broken down

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[7] In light of the Court's recent ruling that Amgen's claims of inducement to infringe will be tried to the Court outside the presence of the jury, Roche limits its discussion to the '933 claims that remain under jury consideration. However, no reasonable Court or jury could conclude that Roche induces infringement of '933 claims 11 and 14, the method of treatment claims, because law is clear that "there can be no inducement of infringement without direct infringement by some party." *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1033 (Fed. Cir. 2002). Moreover, inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). Amgen has no evidence of direct infringement because none exists -- Amgen cannot contend otherwise. Accordingly, judgment as a matter of law on these claims is proper.

[8] Claim 3 of the '933 patent is a product-by-process claim which reads: "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." Claims 7 and 8 further refine claim 3 by limiting the host cell to a "non-human mammalian host cell" and a "CHO cell," respectively. Moreover, claim 9 reads: "A pharmaceutical composition comprising an effective amount of a glycoprotein product for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier." Claim 12 is exactly the same as claim 9 except that it depends from claim 7 instead of claims 1-6. Finally, claims 11 and 14 depend from claims 9 and 12, respectively, and call for a method of treating kidney dialysis patients with said pharmaceutical compositions to increase their hematocrit. Amgen has not proven that Roche literally infringes any of these claims, nor does the evidence support such a conclusion. (TRX 1).

into its starting materials. "In fact, the linkage of peg to EPO is exactly the same chemical bond that links alanine and any other amino acid to every other amino acid in a protein. It's the same amide bond." (Lodish 2516:10-15). Accordingly, the synthetic procedures employed to make CERA result not in a molecule "containing" epoetin beta and mPEG-SBA, but rather "one molecule" that is the result of chemical modification and material changes in structure. (Lodish 2514:14-19).

Moreover, as explained above, CERA is not and does not contain the product of the expression of a DNA sequence encoding human erythropoietin, i.e., a "protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." Dr. Lodish plainly admitted that the amino acid sequence of CERA is different than the amino acid sequence of human EPO, due to chemical modifications at the point of attachment. (Lodish 2510:7-2514:7). Dr. Lodish admitted that his own textbook classifies such chemical modifications as the formation of a "different" amino acid. (Lodish 2522:7-16). Accordingly, even if, as Amgen erroneously asserts, the alleged infringing product is the epoetin beta "contained in" CERA, the amino acid sequence has *different* residues than EPO, as Dr. Lodish admitted. *See Lilly*, 82 F.3d at 1570 (finding that the substitution of a hydroxy group with a chlorine group resulted in a new compound).

Furthermore, Roche's epoetin beta starting material -- as opposed to CERA -- cannot be the glycoprotein product of the claims. Claim 3 recites a "*non-naturally occurring* glycoprotein product," which the Court has construed as meaning "not occurring in nature." (D.I. 613 at 32). Amgen has failed to show -- and indeed cannot show -- that epoetin beta is distinguishable from naturally-occurring EPO and thus does not occur in nature. Furthermore, Roche does not make, use, sell or offer for sale epoetin beta. Rather, epoetin beta is used as a starting material for CERA, the active ingredient in MIRCERA.

Therefore, no reasonable jury could conclude that Amgen has satisfied its burden of proving that Roche makes, uses, sells or offers for sale in the United States a product that satisfies literally each and every element of claims 3, 7 or 8 of the '933 patent.

**b. Amgen Has Not Proven That Roche Infringes The Pharmaceutical Composition Claims Of The '933 Patent**

In light of the undisputable conclusion that Roche does not infringe claims 3, 7 or 8 of the '933 patent, Roche cannot infringe the pharmaceutical composition claims that depend from these claims -- namely, claims 9 and 12. Even if the Court nonetheless finds that a reasonable jury could conclude that Roche infringes claim 12, Roche is entitled to judgment as a matter of law regarding the alleged infringement of claim 9 because Dr. Lodish's claim-by-claim infringement testimony made no mention of '933 claim 9. (*See, e.g.*, Lodish 2394:25-2395:13). Accordingly, without any supporting evidence or testimony, no reasonable jury could conclude that Roche infringes claim 9.

In sum, Amgen has not presented sufficient evidence for a reasonable jury to conclude that Roche's MIRCERA product literally infringes any of the asserted claims of the '933 patent.[9]

**2. No Reasonable Jury Could Find That Roche's MIRCERA Product Infringes The Asserted Claims Of The '933 Patent Under The Doctrine**

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[9] Even if literal infringement could be found as to any of these claims -- which it cannot -- the reverse doctrine of equivalents warrants judgment as a matter of law in Roche's favor. [T]he purpose of the 'reverse' doctrine is to prevent unwarranted extension of the claims beyond a fair scope of the patentee's invention." *Scripps Clinic & Research Found v. Genentech Inc.*, 927 F.2d 1565, 1581 (Fed. Cir. 1991). "[T]he Court must determine the originally intended scope, the 'spirit and intent' of the claims, based on the context of the patent, the prior art, and the particular circumstances of the case." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 285 (D. Mass. 2004) (citations omitted). The fact remains that the Patent Office granted Roche a patent on its novel and nonobvious product, which this Court has held "may aid in making a *prima facie* case in support of the reverse doctrine of equivalents." *Id.* at 300; *Jewish Hosp. of St. Louis v. IDEXX Labs.*, 973 F. Supp. 24, 28 (D. Me. 1997). Moreover, as discussed above, there are numerous differences between MIRCERA and the asserted claims of the patents-in-suit. These facts are sufficient to make out a *prima facie* case. *Amgen, Inc.*, 339 F.3d at 295 (acknowledging that "a difference in biological activity or therapeutic effects" is relevant proof regarding the reverse doctrine of equivalents). Given that Amgen has presented no evidence in rebuttal to Roche's *prima facie* case, the only conclusion is that even if a reasonable jury could find that Roche literally infringes any of the asserted claims, no reasonable jury could find that Roche does not prevail under the reverse doctrine of equivalents.

**Of Equivalents**[10]

**a. Legal Standards**

A product "which does not infringe a patent claim literally may still infringe the claim under the doctrine of equivalents if each and every limitation of the claim is literally or equivalently presented." *Amgen, Inc.*, 126 F. Supp. 2d at 117 As this Court explained: "A claim limitation is equivalently present in an accused product if there are only 'insubstantial differences' between the limitation and the corresponding aspects of the product. 'The usual test of the substantiality of the differences is whether the element in the accused composition performs substantially the same function in substantially the same way to obtain substantially the same result as the claimed element.'" *Id*. (citations omitted).

This Court further observed that "application of infringement by equivalents ... is limited by the doctrine of prosecution history estoppel." *Id*. According to the Federal Circuit "[t]he doctrine of prosecution history estoppel acts as a 'legal limitation on the doctrine of equivalents.' '[P]rosecution history estoppel limits the range of equivalents available to a patentee by preventing recapture of subject matter surrendered during prosecution of the patent.'" *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 2007 WL 1932269, *6 (Fed. Cir. 2007).

The Supreme Court has "made clear that a 'presumption' of prosecution history estoppel arises when an amendment is made to secure the patent and the amendment narrows its scope." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126, 131 (D. Mass. 2003) (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 535 U.S. 722, 736 (2002)). "The inventor

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[10] Although Amgen has presented no evidence on the doctrine of equivalents as to the process claims of the '868, '698 and '349 patents, there is no basis as a matter of law for applying the doctrine of equivalents to alleged infringement under 35 U.S.C. § 271(g). (*See* D.I. 1358). In light of the utter lack of evidence regarding equivalency for the asserted process claims, in conjunction with the fact that there appears to be no basis in law for such an argument, Roche limits its analysis on the doctrine of equivalents to the claims of the '933 patent.

can overcome the 'presumption' by showing that the amendment does not surrender the particular equivalent in question." *Id*. There are three "narrow ways" of rebutting the presumption of estoppel: (i) "showing that an equivalent was unforeseeable; (ii) demonstrating that the purpose of an amendment was merely tangential to the alleged equivalent; or (iii) establishing 'some other reason' that the patentee could not have reasonably been expected to have described the alleged equivalent." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1310-11 (Fed. Cir. 2006); *see Cross Med. Prods. Inc. v. Medtronic Sofamor Danek Inc.*, 480 F.3d 1335, 1342 (Fed. Cir. 2007) ("[The t]angential relation criterion for overcoming the *Festo* presumption is very narrow.").

**b. Amgen Is Estopped From Arguing Doctrine Of Equivalents Pursuant To *Festo*[11]**

As explained above, Roche does not literally infringe any of the claims of the '933 patent because neither CERA nor MIRCERA is a glycoprotein product covered by the asserted claims. Nevertheless, Amgen has, in the past, argued that CERA and MIRCERA contain insubstantial equivalents of the asserted claim limitations. Amgen, however, is precluded as a matter of law from maintaining this position. (*See* D.I. 621).

During the prosecution of the '933 patent, Amgen sought numerous claims to polypeptides having "part or all of the primary structural conformation ... of naturally-occurring erythropoietin" or "having a primary structural conformation sufficiently duplicative of that of a naturally-occurring human erythropoietin." (*See* TRX 2011.106, 110-111 (file claims 1, 7, 41 and 48)). These claims

[11] Similarly, Amgen is estopped from asserting the doctrine of equivalents for the asserted claims of the '868 and '698 patents. While Roche limits its estoppel arguments in this memorandum to the '933 patent, Roche incorporates by reference its prior submissions regarding prosecution history estoppel as to the asserted claims of the '868 and '698 patents. (*See* D.I. 624, 625, 626). Accordingly, even if the Court finds that the doctrine of equivalents applies to infringement under § 271(g) -- although there is no basis in law for such a finding -- the utter lack of evidence in conjunction with the clear unrebutted evidence of prosecution history estoppel mandates a directed verdict in Roche's favor on this issue.

were rejected, and the examiner noted that that the terms "part or all of" and "sufficiently duplicative of" "do not particularly nor adequately point out the distinctions from native erythropoietin (EPO)." (TRX 2011.158-160). In other words, these claims were indefinite. Moreover, the examiner stated that "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." (TRX 2011.160).

In response to these rejections, Amgen cancelled claims 1, 7 and 48 and amended claim 41, keeping the "sufficiently duplicative" language. (TRX 2011.172). After further rejections, Amgen cancelled claim 41 and substituted a new claim 67, a product-by-process claim, which also contained the same "sufficiently duplicative" language. (TRX 2011.249). Amgen noted that the recombinant erythropoietin in its claims could not be "precisely defined except by the process by which it is produced." (TRX 2011.251). The examiner maintained his Section 112 rejection based on the "sufficiently duplicative" language. (TRX 2011.260). Ultimately, Amgen cancelled claim 67 in favor of new claim 76, which did not contain the "sufficiently duplicative" language, and added the claim limitation: "product of the expression of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin." (TRX 2011.288). Amgen noted that the new claim was "similar" to the cancelled claims but "specify that the DNA sequences encode human erythropoietin." (TRX 2011.292). Eventually, claim 3 of the '933 patent issued without any limitation to "sufficiently duplicative" or "having part or all of the primary structural conformation."

Based on the repeated rejections it faced, Amgen deliberately chose to prosecute the '933 patent without claim limitations "having part or all of the primary structural conformation" or "sufficiently duplicative." Specifically, by removing these limitations and incorporating the

limitation "DNA sequence encoding human erythropoietin," Amgen narrowed the asserted claims to cover only human erythropoietin in accordance with the examiner's repeated determinations that broader claims were not supported by the disclosure. Moreover, by choosing to transform its claims to product-by-process claims in accordance with the examiner's rejections, Amgen cannot claim anything other than the actual product of the process -- not alleged equivalents.

Amgen has presented no evidence whatsoever to rebut the presumption of prosecution history estoppel. *See Pioneer Magnetics, Inc. v. Micro Linear Corp.*, 330 F.3d 1352, 1356 (Fed. Cir. 2003) ("[w]here no explanation [for amending the claim] is established, a court should presume that the applicant had a substantial reason related to patentability for the amendment"). Accordingly, the '933 claims are limited to the amino acid sequence disclosed in Figure 6 (i.e. 166 amino acids) and do not encompass fragments, analogs or synthetic polypeptides under the doctrine of equivalents. Even under the alternative definition of human EPO as the 165 amino acid sequence of EPO isolated from urine, Amgen's narrowing amendments preclude it from claiming products other than human EPO, including CERA, which has a different amino acid sequence than the asserted claims.

**c. Amgen's Failure To Conduct An Element-By-Element Analysis Under The Doctrine Of Equivalents Forecloses A Finding Of Infringement**

Even if Amgen is not estopped from asserting the doctrine of equivalents with respect to the asserted claims of the '933 patent, Amgen cannot, as a matter of law, prevail on this issue. As the Court recognized during trial, the law is clear that to prevail on a claim under the doctrine of equivalents, the patentee must perform an element-by-element analysis to show that each individual element of the asserted claim is found in the accused device, either literally or by equivalency. *Lemelson v. United States*, 752 F.2d 1538, 1551 (Fed. Cir. 1985); (*see also* Trial Tr. 2484:2-13). Amgen produced no evidence and elicited no testimony relating to an element-by-element analysis

of any of the asserted claims. Indeed, the Court, and even Amgen, recognized that Amgen failed to put Roche on notice of any claim-by-claim analysis and, accordingly, was foreclosed from presenting a case of infringement doctrine of equivalents. (Trial Tr. 2484:2-2486:3). After the Court cautioned Amgen that Dr. Lodish's report would be insufficient to meet the Federal Circuit's requirements, Amgen simply moved on to a new topic. (Trial Tr. 2486:1-3). The utter lack of appropriate evidence on this issue mandates a directed verdict in Roche's favor.

Even if Amgen had attempted to present evidence on the doctrine of equivalents, Amgen could not have met its burden because any alleged "equivalent" employed by Roche imparts substantially different function and properties to MIRCERA. For example, as explained above, MIRCERA has a longer half life and lower binding affinity than Amgen's claimed EPO product. Faced with a very similar situation regarding t-PA, the Federal Circuit held in *Genentech, Inc. v. Wellcome Foundation Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994), that the function prong of the doctrine of equivalents cannot be defined so broadly otherwise it would be "difficult to imagine how ... any version of t-PA ... would avoid infringement under the doctrine of equivalents because t-PA ... would by definition necessarily perform this function in the same general way with the same general results." *Id.* at 1567. The court therefore reversed a jury verdict of infringement under the doctrine of equivalents based on differences in binding affinity and half-life because "the results achieved are hardly substantially the same." *Id.* at 1569. Similarly, in *Amgen, Inc. v. Chugai Pharm. Co.*, the court expressly held that Amgen is not entitled to any and all EPO analogs, noting that Amgen's patents do not cover everything that has "EPO-like activity." 927 F.2d 1200, 1214 (Fed. Cir. 1991).

Furthermore, the evidence shows that during prosecution of the patents-in-suit, Amgen argued to the PTO that human erythropoietin is an "obligate glycoprotein," a term Amgen coined to mean that EPO must be properly glycosylated to possess *in vivo* activity. (TRX 2012.219) Amgen

stated that the claimed processes were "believed to constitute one of the first instances (if not the first instance) of recombinant production of an *in vivo biologically active obligate human glycoprotein*." (*Id*.) (emphasis in original). Amgen has failed to introduce any evidence that CERA is likewise an "obligate glycoprotein" and, indeed, the evidence will show otherwise.

In accordance with the clear principles of law and Amgen's utter lack of evidence, the Court should grant a directed verdict on the doctrine of equivalents.

## IV. CONCLUSION

For the foregoing reasons, Roche respectfully requests that the Court grant judgment as a matter of law that Roche does not infringe any of the asserted claims of the patents-in-suit.

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CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) on the above date.

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