IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE, LTD, ROCHE DIAGNOSTICS GmbH, HOFFMANN-LA ROCHE INC., Defendants.	Civil Action No. 05-12237 WGY U.S. District Judge Young *Leave to file granted on 10/4/07*

ROCHE'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW REGARDING INVALIDITY

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*)
Peter Fratangelo (BBO# 639775)
Krista M. Rycroft (*pro hac vice*)
Kaye Scholer LLP
425 Park Avenue
New York, New York 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.

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

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 regarding their defenses of invalidity.[1] Roche has presented substantial evidence to allow a reasonable jury to conclude by clear and convincing evidence that each asserted claim is invalid. Moreover, Amgen has presented no competent evidence to defeat Roche's clear and convincing evidence. Accordingly, a reasonable jury could be led to make just one conclusion: the claims-in-suit are invalid.

- Claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent, all product-by-process claims, are anticipated pursuant to §§ 102(a), 102(b) and 102(g)[2]: The Baron-Goldwasser clinical trial in 1979, Dr. Essers' studies in 1973-75, Dr. Eschbach's clinical study in 1984, Dr. Fritsch's work at Genetics Institute and the Miyake publication independently anticipate every claim limitation, as confirmed by the testimony of Drs. Lowe, Spinowitz, Baron, Goldwasser and Bertozzi. Other than the conclusory testimony of its paid experts that squarely contradicts Amgen's own prior admissions, Amgen has presented no evidence to defeat the clear and convincing teachings of these prior art references. Moreover, the law is crystal clear that anticipation by an earlier product disclosure cannot be avoided by claiming the product as produced by a particular process or from a particular source. Amgen has presented no evidence to sustain its burden of showing that the process or source of production imparts novel structural features to its claimed products.

- Claim 1 of the '422 patent and claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent also would have been obvious to one of skill in the art in light of the prior art studies by Drs. Baron and Goldwasser, Dr. Essers and Dr. Eschbach. Amgen presented no competent evidence to defeat Roche's clear and convincing evidence on this issue.

- The asserted claims of the patents-in-suit are obvious pursuant to 35 U.S.C. § 103, § 102(f)/§ 103 and § 102(g)/§ 103 in light of the prior art. There is substantial evidence that every element of the asserted claims was known in the prior art and one of ordinary skill in

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[1] Similarly, this memorandum serves as an opposition to Amgen's motion for judgment as a matter of law. (D.N. 1136, 1137-2, 1270). While Roche hereby recapitulates the evidence presented at trial pertaining to its invalidity defenses, Roche also incorporates by reference the evidence and arguments set forth in its Opposition to Amgen's Motion for Judgment as a Matter of Law, and accompanying papers. (*See* D.N. 1141, 1142, 1144, 1145, 1146, 1148).

[2] Roche respectfully maintains its position that claim 1 of the '422 patent is similarly invalid for anticipation. However, in light of the Court's ruling that claim 1 is not anticipated as a matter of law, (Trial Tr. 1380:7-12), Roche limits its arguments in this memorandum to the related claims of the '933 patent.

the art was motivated to combine these elements, such that each claim would have been obvious in the 1983-84 time period. Substantial evidence has demonstrated that subject matter "critical" to each of these claimed inventions was derived from the work of Dr. Goldwasser, as admitted by Drs. Goldwasser, Orkin and Lin, and confirmed by Dr. Lowe. This subject matter, which includes Table 1 of Example 1 of Lin's patent specification, in combination with the prior art would have rendered each of the asserted claims obvious to one of ordinary skill in the art in 1984. Amgen presented no relevant evidence to defeat Roche's clear and convincing evidence. Each of Amgen's witnesses presented conclusory testimony that was squarely contradicted by the prior art and their own prior non-litigation-driven admissions.

- Claim 1 of the '422 patent, claims 1-2 of the '868 patent, claims 6-9 of the '698 patent, claim 7 of the '349 patent and claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent are invalid for lack of written description and/or indefiniteness pursuant to § 112 based on the limitation "human erythropoietin," as explained by Drs. Bertozzi and Flavell.[3]

- Claim 7 of the '349 patent is invalid pursuant to § 112 because it lacks enablement regarding its claim limitation of using radioimmunoassay (RIA) to measure the production of human erythropoietin expressed by vertebrate host cells. As confirmed by Dr. Flavell's testimony, RIA cannot distinguish "erythropoietin" from fragments, non-human EPO and other cross-reacting substances.

- Claim 7 of the '349 is invalid for lack of written description and non-enablement of the term "vertebrate cells." There can be no dispute that vertebrate cells covers a broad class of cells, including mammalian cells, reptile cells, amphibian cells, bird cells and fish cells. Yet, the common specification of the patents-in-suit only mention COS and CHO cells, two discrete species mammalian cells. Amgen's own witnesses, including Drs. Lin and Varki, admit that different host cells have different properties and have mixed results in terms of protein expression. Accordingly, any description or enablement of CHO or COS cells -- to the extent such description is even present in the specification -- cannot amount to description of the much broader genus of vertebrate cells. There has been no evidence to counter these facts.

II. LEGAL STANDARDS

A. Judgment as a Matter of Law Pursuant to Fed. R. Civ. P. 50

"[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

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[3] Roche respectfully maintains that claims 3, 7, 8 and 11 of the '933 patent are similarly invalid for lack of written description based on the term "human erythropoietin." In light of the Court's ruling that these claims are not invalid for lack of written description as a matter of law, (Trial Tr. 1380:7-12), Roche limits its arguments in this memorandum to the remainder of the asserted claims. However, because the Court made no rulings on indefiniteness, Roche still maintains that claims 3, 7, 8 and 11 of the '933 patent are invalid for indefiniteness.

"'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). Where, as here, the movant bears the burden of proof, JMOL may be granted where "(1) the movant 'has established [its] case by evidence that the jury would not be at liberty to disbelieve' and (2) 'the only reasonable conclusion is in [the movant's] favor.'" *Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1065 (Fed. Cir. 1998). To warrant submission of these issues to the jury, Amgen must have presented "more than a mere scintilla" of evidence and may not simply rely on conjecture or speculation. *Richmond Steel, Inc. v. Puerto Rican Am. Ins. Co.,* 954 F.2d 19, 22 (1st Cir. 1992). As the record clearly establishes, Amgen's evidence supporting validity is, at best, a "mere scintilla."

B. Clear And Convincing Evidence Is Not An Insurmountable Burden

Amgen has, in the past, argued that Roche cannot meet its burden of providing clear and convincing evidence, characterizing the burden as essentially insurmountable. However, "under the 'clear and convincing' standard, proof need not be airtight. The law requires persuasion, not perfection." *Buildex Inc. v. Kason Indus., Inc.,* 849 F.2d 1461, 1464 (Fed. Cir. 1988). "Although an exact definition is elusive, 'clear and convincing evidence' has been described as evidence that 'place[s] in the ultimate fact finder an abiding conviction that the truth of its factual contentions are highly probable.'" *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1360 n.5 (Fed. Cir. 2007); (*see also* D.N. 1141-4). Not only has Roche more than met its burden, no reasonable jury could conclude that Amgen presented any competent evidence to rebut the only clear and convincing conclusion: that Roche must prevail.

Amgen argues that because certain of the references relied upon by Roche to support its obviousness and anticipation defenses were submitted to the PTO examiner, Roche has a heightened burden in rebutting the presumption of validity afforded to patents. Amgen is wrong.

See Pfizer, Inc., 480 F.3d at 1359-60 ("presumption [of validity] remains intact and [the burden of proof remains] on the challenger throughout the litigation, *and the clear and convincing standard does not change*") (emphasis added). As an initial matter, not all references relied upon by Roche were submitted to the PTO examiner, including highly relevant pages of the Maniatis manual (TRX 10) and documents pertaining to the Baron-Goldwasser study, among others. Moreover, the references that were submitted to the examiner were buried among hundreds of references that the examiners reviewed in one or two days. (*See, e.g.*, TRX 2009.558-595 (reviewing 436 references in 1 day), 2012.951-977 (reviewing 372 references in 1 day), 2007.177-206 (reviewing 437 references over 2 days), 2011.515-540 (reviewing 390 references over 2 days), 2017.240-268 (reviewing 437 references over 2 days); *see also* M.P.E.P. § 609.05(b) (8th ed. Aug. 2001) ("[t]he examiner must also fill in his or her name and the date the information was considered"); *Bausch & Lomb, Inc. v. Alcon Labs., Inc.*, 79 F. Supp. 2d 252, 255 (W.D.N.Y. 2000) (If there is "evidence that there actually were defects in the particular application process at issue in this case, thus suggesting that deference to the PTO's determination may not be appropriate," such evidence may be relevant to overcoming the presumption of validity). Accordingly, despite Amgen's contention, even if some -- or even all, as Amgen erroneously contends -- of the references relied upon by Roche were submitted to the PTO examiner, Roche's burden does not change and all relevant evidence must be considered. *See Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984) ("[a]ll evidence bearing on the validity issue, *whether considered by the PTO or not*, is to be taken into account by the tribunal in which validity is attacked"); *see also A.K. Steel Corp. v. Sollac*, 344 F.3d 1234, 1245 (Fed. Cir. 2003) ("the presumption is far from determinative").

C. The Burden of Proof Does Not Rest Solely With Roche

Despite Amgen's repeated suggestion, Roche does not carry all the weight in the invalidity portion of this trial.

The asserted claims of the '933 patent are indisputably product-by-process claims. Similarly, '422 claim 1 contains a source limitation. The law makes clear that recitation of source or process limitations such as "non-naturally occurring," "product of the expression ... in a mammalian host cell" or "purified from mammalian cells grown in culture" does not distinguish product-by-process claims over the prior art unless the source or process imparts unique structure to the product. *SmithKline Beecham Corp. v. Apotex Corp*., 439 F.3d 1312, 1317 (Fed. Cir. 2006); *Amgen Inc v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003).[4] "Where a product-by-process claim is rejected over a prior art product that appears to be identical, ... the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product." *In re Marosi*, 218 U.S.P.Q. 289, 293 (Fed. Cir. 1983); *see also In re Moeller*, 117 F.2d 565, 567 (C.C.P.A. 1941).

Moreover, to defeat Roche's clear and convincing evidence of *prima facie* obviousness, Amgen relies on secondary considerations of non-obviousness, such as long felt need. The law makes clear that Amgen has the burden of proving a sufficient nexus between its satisfaction of a long felt need and the patents-in-suit. *See WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999) ("[t]he patentee bears the burden of showing that a nexus exists between the claimed features of the invention and the objective evidence offered to show nonobviousness"); *see also B.E. Meyers & Co. v. United States*, 47 Fed. Cl. 375, 378 (Fed. Cl. 2000) (same).

Finally, Amgen has the burden of proving a date of conception prior to November 30, 1984. The date of invention for prior art purposes is the filing date of the application until an earlier date is proved. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986). To establish an earlier filing date, Amgen had to "present evidence of its asserted actual

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[4] *See* Roche Motions in Limine D.N. 1047 and 1046; *see also* D.N. 1141-5.

reduction to practice prior to the filing date of its patent application." *Loral Fairchild Corp. v. Matsushita Elec. Indus. Co.*, 266 F.3d 1358, 1361 (Fed. Cir. 2001). Amgen has presented no evidence to meet its burden. Accordingly, the critical date for assessing anticipation is November 30, 1984. Moreover, the 1984 filing date is a later date of invention than in *Amgen v. Chugai*, 13 U.S.P.Q.2d 1737 (D. Mass. 1989), making any findings regarding obviousness in that case irrelevant here due to, *inter alia*, the advances in the prior art during the intervening time period together with the standard for obviousness under the present law. *See KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007); (*see also* D.N. 1070-2, 1146).

III. THE ONLY CONCLUSION THAT A REASONABLE JURY COULD REACH IS THAT CLAIMS 3, 7-9, 11, 12 AND 14 OF THE '933 PATENT ARE ANTICIPATED

A. Anticipation and Prior Invention Under § 102(a), (b) and (g)

As to Roche's claim that claims 3, 7-9, 11, 12 and 14 are invalid as anticipated, a reasonable jury could only find in Roche's favor, as Roche has presented clear and convincing evidence that each and every element of these claims is present in a single prior art reference. *Holdings, LLC v. Amazon.com, Inc.*, 430 F.3d 1377, 1381 (Fed. Cir. 2005). Amgen presented no evidence to rebut this clear conclusion.

B. Level of Skill in the Art

The evidence has shown that a person of ordinary skill in the art in the period 1983-84 was someone who has earned a M.D. or Ph.D degree and who has one or two years of post-graduate laboratory research experience. (Lowe 193:8-12; Bertozzi 1061:19-25; Spinowitz 768:16-19). It is from this person's understanding and perspective that the prior art and obviousness must be judged. *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006).

C. '933 Claims 3, 7 and 8 Are Invalid For Anticipation

Roche presented clear and convincing evidence such that a reasonable jury could only conclude that claims 3, 7 and 8 are invalid for anticipation over Dr. Goldwasser's prior art EPO

purified from human urine. As noted above, because source and process limitations cannot confer patentability to an otherwise non-novel product, Amgen must show that these limitations confer a novel structure.

Amgen has presented wholly insufficient evidence to contradict the presumption that the source and process limitations in claim 3 are irrelevant.[5] Even if, as Amgen suggests in direct contradiction of established principles of law, this burden should fall on Roche, Dr. Bertozzi presented clear and convincing evidence demonstrating that "Goldwasser's EPO has structures that can all be made according to claim 3. So the product of claim 3 is basically the same as Goldwasser's EPO." (Bertozzi 1018:13-15; Bertozzi 988:19-21 ("nothing distinguishes them. The EPO that comes from mammalian cells in culture is *the same*, the molecules are *the same* as Goldwasser's EPO") (emphasis added); *see also* Bertozzi 1027:20-1028:2, 1028:15-18, 1146:23-24 (there is a "statistical certainty" that the molecules of the prior art EPO and the claimed recombinant EPO have the same structure)). For example, Dr. Bertozzi showed that different lots of recombinant EPO submitted for regulatory approval by Amgen have a range of specific activity that spans the reported specific activity for Dr. Goldwasser's EPO glycoproteins. (Bertozzi 1159:1-1161:2). Dr. Strickland, Amgen's witness, confirmed these conclusions, and agreed that his own patent recognized as much. (Strickland 2157:12-2159:4; *compare* TRX 2104 with TRX 2002). Moreover, Amgen's own PLA and published articles confirm Dr. Bertozzi's opinions:

- Amgen's PLA states that "[t]his gene, when inserted into mammalian cells, yields a recombinant product that is immologically and biologically *indistinguishable* from naturally derived erythropoietin." (TRX 2056 at AM-ITC 00092263 (emphasis added); Bertozzi 1032:7-1033:1). It further states that "[a]ll physical tests performed on both r-HuEPO and u-HuEPO as discussed in this Section show these proteins to be *indistinguishable*, as

[5] Claims 7 and 8 limit the "mammalian host cell" limitation of claim 3 to a "non-human mammalian cell" and a "CHO cell," respectively. For the same reasons, these limitations do not serve to confer patentability to claims 7 and 8.

summarized below." (TRX 2057 at AM-ITC 00092880; Bertozzi 1034:5-1035:5, 1036:20-1037:9).

- A 1986 publication by Amgen personnel, including Drs. Lin, Strickland, Egrie and Browne, states "As seen in Figure 4, purified recombinant human erythropoietin migrates identically to human urinary erythropoietin with an apparent molecular weight of approximately 36,000 daltons, *suggesting that both molecules are glycosylated to the same extent*." (TRX 2058 at p. 218 (emphasis added); Bertozzi 1038:15-1039:18). Another 1986 publication by the same Amgen personnel contains similar conclusions. (TRX 2059 at p. 698; Bertozzi 1042:6-18).

- A 1984 presentation by Amgen's Dr. Egrie similarly concludes that "COS cells [which are covered by claims to mammalian cells] transfected with the human EPO gene produce and secrete fully glycosylated EPO which migrates identically to the human EPO standard." (Bertozzi 1043:23-1044:22; TRX 2060). A 1985 publication by Amgen personnel, including Drs. Egrie, Browne, Lin and Lai, contains similar conclusions. (TRX 2061; Bertozzi 1045:23-1046:1).

- A 1988 publication by Amgen personnel, including Drs. Vapnek, Egrie, Browne, Lin and Strickland, concludes "[i]n all physical measurements made to date, the natural material *cannot be distinguished* from the recombinant material." (TRX 2062 at p. 249 (emphasis added); Bertozzi 1047:7-14).

Accordingly, pursuant to the testimony of Dr. Bertozzi and Dr. Strickland and corresponding documentary evidence, a reasonable jury could be led to only one conclusion: that claims 3, 7 and 8 of the '933 patent are anticipated by Dr. Goldwasser's prior art urinary EPO. (*See* Bertozzi 1048:2-6, 1048:8-9).[6] Moreover, as explained below, numerous studies using pharmaceutical compositions comprising EPO that cannot be shown to be structurally distinct from the EPO claimed in claims 3, 7 and 8 also render these claims invalid for anticipation. *See Lewmar Marine, Inc. v. Barient, Inc.*,

[6] Moreover, evidence from Dr. Edward Fritsch of Genetics Institute ("G.I.") demonstrated that G.I. cloned an EPO cDNA, transfected it into COS and CHO cells and expressed high levels of *in vitro* and *in vivo* biologically active human EPO. As Amgen acknowledges, all of this work was completed before November 30, 1984, the effective filing date of Amgen's patents, and thus constitutes prior art under Section 102(g) that was not abandoned, suppressed or concealed since this work was published in February 1985. (*See* Fritsch 350:19-360:21; *see also* TRX 2090, 2084). Accordingly, a reasonable jury could only conclude that even if the source and process limitations confer structural distinctiveness to Amgen's claimed product, Dr. Fritsch's prior work anticipates claims 3, 7 and 8 of the '933 patent.

827 F.2d 744, 747 (Fed. Cir. 1987) ("[t]hat which would *literally* infringe if later in time anticipates if earlier") (emphasis in original).

Amgen presented no competent evidence to rebut the clear conclusion that there is no structural difference between Dr. Goldwasser's urinary EPO and EPO produced in mammalian cells. Amgen's claims are directed to *any* EPO glycoproteins that can be produced in *any* mammalian host cells, under *any* conditions, in *any* populations, with *any* specific activity and purified in *any* way. All of the experiments discussed by Dr. Varki compared urinary EPO to a limited number of samples of recombinant EPO produced in mammalian cells. As Dr. Varki readily acknowledged, there are at least 30,000 different types of mammalian cells, not including mutated mammalian cells, all of which would fall within the scope of the claim limitation to "mammalian cells." (Varki 2247:16-22). He further acknowledged that these different types of cells can have different properties in terms of creating recombinant EPOs depending on many factors including mutations, pH, nutrient conditions and purification techniques. (Varki 2249:5-10). Yet, Dr. Varki limited his analysis to only *three* mammalian cells, at most, out of at least 30,000 choices. (Varki 2251:9-17). The law is clear that patentability can not be shown simply by showing differences between one embodiment of a claim and the prior art. The entire scope of the claim must be distinct from the prior art. *See Jackson Jordan, Inc. v. Plasser Am. Corp.*, 747 F.2d 1567, 1578 (Fed. Cir. 1984); *OKI Am., Inc. v. Adv. Micro Devices, Inc.*, 2006 WL 2711555, *6 (N.D. Cal. Sept. 21, 2006).

Aside from the fact that Dr. Varki's analysis was limited to a mere subset of the claimed products, he discussed SDS-PAGE experiments comparing recombinant EPO to urinary EPO and repeatedly admitted that many SDS-PAGE experiments do not show any structural difference. (Varki 2188:2-25, 2193:6-8). The best explanation that Dr. Varki could proffer was simply that just because no difference was shown in those experiments, "that does not mean the difference does not exist." (Varki 2193:6-8). This is hardly sufficient for Amgen to meet its burden in demonstrating

structural distinctiveness. Moreover, Dr. Varki's discussion of Dr. Strickland's IEF experiments, which are not even described in the patents, was based on the *assumption* that the experiment tested Amgen's recombinant EPO. (Varki 2206:5). Even if this assumption was correct, as discussed above, the results of the experiment are insufficient to establish that the broad range of recombinant EPOs covered by Amgen's claims are *all* different than Dr. Goldwasser's EPO. Similarly, the Dionex experiments relied upon were also based on the assumption that the urinary EPO was Dr. Goldwasser's EPO that was being compared to what Dr. Varki assumed to be one sample of recombinant EPO within the broad spectrum of recombinant EPOs within the scope of Amgen's claims. (Varki 2213:17-20, 2214:20-21). Even if the Dionex test showed a conclusive difference -- which it did not -- Amgen cannot rely on this test to show what was known in 1984 because this test was not available at the time. *See Nat'l Research Development Corp. v. Great Lakes Carbon Corp.*, 410 F. Supp. 1108, 1124 (D. Del. 1975) ("[t]o satisfy the statue, there must have been a test available at the time of the filing of the patent application which could have been employed by a person skilled in the art"); *In re Wright*, 999 F.2d 1557, 1563 n.8 (Fed. Cir. 1993); *see also* D.N. 1274.

Accordingly, as Amgen has not proven any structural distinction based on source and process claims, a reasonable jury could only conclude that these claims are invalid.

D. '933 Claims 9, 11, 12 And 14 Are Invalid For Anticipation

Roche presented the jury with substantial testimony and documentary evidence that at least four separate pieces of prior art anticipate '933 claims 9, 11, 12 and 14. Amgen provided no credible evidence in rebuttal. These claims are limited to pharmaceutical compositions and methods of using these pharmaceutical compositions to treat kidney dialysis patients and increase hematocrit.

1. The Baron-Goldwasser Clinical Study

Dr. Spinowitz explained that the 1979-1980 Baron-Goldwasser study shows administration of a pharmaceutical composition of human EPO comprising a diluent, suitable for human administration.[7] (Spinowitz 706:9-11, 707:1-9, 705:20-706:1, 707:23-708:16; TRX 2004). The human EPO in this composition is the same human EPO that renders claims 3, 7 and 8 anticipated, as discussed above. This pharmaceutical composition further comprised a therapeutically effective amount of human EPO because, after administration to patients, it elicited a measurable reticulocyte response, an increase in the number of nucleated red blood cells in the bone marrow, an increase in red blood cell mass, and positive ferrokinetic effects including a decrease in radioactive iron in plasma indicating that iron was being used to form new red blood cells. (Spinowitz 711:3-712:12, 713:17-714:3, 715:19-716:19, 718:15-22, 719:7-18; Baron 671:8-21; TRX 2004, 2045, 2049). These responses each report the stimulation of red blood cell formation.[8]

Moreover, Amgen reported to the FDA in its Epogen® IND filing that based on prior art studies, "[t]herapy with erythropoietin has been shown to be effective in selected patients with ESRD."[9] (TRX 2054 at p. 4; Spinowitz 790:24-791:9, 792:3-23; Friedman 1475:4-12). Amgen's own expert, Dr. Friedman, acknowledged that he previously testified under oath that this statement referred to the Baron-Goldwasser study and that when Amgen used the word "effective," Amgen

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[7] The Baron-Goldwasser study is prior art under Sections 102(a), 102(b), 102(f) and 102(g)(2). (*See* D.N. 1141-5; 10/1/07 Electronic Order denying D.N. 1202).

[8] Importantly, these responses are entirely consistent with the Court's claim construction:

> a therapeutically effective amount is one that elicits ***any one*** or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 and 22, stimulation of reticulocyte response, development of ferrokinetic effects (such plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals

(emphasis added). *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 494 F. Supp. 2d 54, 67 (D. Mass. 2007).

[9] ESRD stands for end-stage renal disease, and is a synonym for chronic renal failure (CRF).

meant "it met one of the criteria stipulated by the judge." (Friedman 1475:4-1476:6, 1477:12-22). The only evidence Amgen has conjured to detract from the clear teachings of the Baron-Goldwasser study is Dr. Friedman's personal opinion regarding the merits of the study, which in no way limits the prior art status. Dr. Friedman appears to argue that the Baron-Goldwasser study is not sufficiently enabling, but this is irrelevant. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d at 1357 (if art is not enabling, it "qualifies as prior art, regardless, for whatever is disclosed therein").

Moreover, Dr. Brugnara's disparaging testimony concerning the teachings of this study have no merit. He admitted that he did not consider the totality of the data in his expert report while, at the same time, admitting that a reasonable scientist would have to consider all the data. (Brugnara 2044:17, 2045:12-18). Indeed, Dr. Baron's data (TRX 2049) is 945 pages long and Dr. Brugnara only had 17 days to review documents and provide "independent" conclusions in a detailed expert report. (Brugnara 2046:1-2047:7). It would have been impossible for him to provide the thorough and complete analysis provided by Drs. Spinowitz, Goldwasser and Baron, all of whom performed an extensive review of the data over several years, and ***at the time***, out of the shadow of litigation, concluded that the Baron-Goldwasser study had been effective in stimulating erythropoiesis in three kidney dialysis patients.[10] Dr. Brugnara admitted that he did not attempt to supplement his meager review of incomplete information from any other source, including Drs. Baron or Goldwasser to understand the basis for their past representations to the federal government and Amgen that the study had achieved its limited goals. (Brugnara 2064:25-2065:3, 2074:16-21). Accordingly, based

[10] Indeed, Dr. Brugnara's expert report indicates that he only reviewed approximately 70 pages of the Baron data in forming his opinions.

on the Baron-Goldwasser study, a reasonable jury could be led to only one conclusion: that claims 9 and 12 of the '933 patent are invalid for anticipation. (Bertozzi 1049:12-1050:7).

Moreover, the Baron-Goldwasser study and related documents lead to the clear conclusion that claims 11 and 14 are invalid for anticipation. Roche's expert Dr. Spinowitz testified without contradiction by Amgen that the Baron-Goldwasser clinical study teaches the administration of a pharmaceutical composition comprising human erythropoietin to patients with chronic renal failure on dialysis. (Spinowitz 705:20-706:1, 769:11-15). Dr. Baron corroborated Dr. Spinowitz's testimony and opinions. (Baron 667:19-22). As a clinical investigator with personal knowledge of the patient responses observed first-hand over 20 years ago, Dr. Baron testified that following the administration of the EPO pharmaceutical composition to patients in his clinical study who were kidney dialysis patients, hematocrit values increased. (Baron 672:6-18; *see also* TRX 2049 at Baron 00858).[11] As Amgen has not provided any rebuttal to this clear evidence, a reasonable jury could only conclude that claims 11 and 14 are invalid for anticipation.[12]

2. Dr. Eschbach's Administration of EPO-Rich Human Plasma

In 1984, Dr. Eschbach infused EPO-rich plasma (a pharmaceutical composition with a pharmaceutically-acceptable diluent) from one human patient into another, and observed an increase in reticulocytes and the movement of radioactive iron into new red blood cells, each an

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[11] Although Dr. Baron wrote that there was "no significant increase in hematocrit" measured in the kidney dialysis patients in his study, (Baron 668:10-12 (emphasis added)), the evidence demonstrates that a hematocrit increase was observed. Because claims 11 and 14 do not include any quantitative or qualitative increase in hematocrit as a claim limitation such a requirement cannot be read into the claim. *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 799 & n. 6 (Fed.Cir.1990) ("Nothing in any precedent permits judicial redrafting of claims"). As a result, any increase in hematocrit, including the increase elicited in the kidney dialysis patients who participated in the Baron-Goldwasser clinical study, provides evidence that would allow a reasonable jury to conclude that claims 11 and 14 of the '933 patent are invalid for anticipation under § 102 (a) or (b). *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1377-78 (Fed. Cir. 2001) (finding claim to a method of administration invalid due to anticipation).

[12] Moreover, as explained above, the Baron-Goldwasser study anticipates claims 3, 7 and 8 of the '933 patent because Amgen cannot show that the source and process limitations in these claims provide structural distinctiveness.

indication that a therapeutically effective amount of human erythropoietin was present in the composition. (Spinowitz 743:1-9, 748:19–749:11, 750:19-751:6).[13] As discussed above, the EPO in Dr. Eschabach's EPO-rich plasma is physically indistinguishable from human erythropoietin created from the processes disclosed in the Lin patents and, accordingly, the source and process limitations in the '933 claims cannot confer patentability. Moreover, Amgen's nephrologist expert, Dr. Friedman, admitted that the Eschbach study showed therapeutic effectiveness in human patients. (Friedman 1485:2-10). Amgen's other expert, Dr. Brugnara, who is not a nephrologist, offered no credible explanation as to why plasma is not a pharmaceutical composition comprising a diluent, adjuvant or carrier, given that Dr. Eschbach administered this preparation to humans with institutional review board approval. (*See* Brugnara 2043:6-10). Accordingly, a reasonable jury would only conclude, based on the unrefuted testimony of Dr. Spinowitz and the Eschbach study, that claims 9 and 12 of the '933 patent are invalid for anticipation.[14]

3. Dr. Essers' Studies Using EPO-Rich Human Plasma

As with the Eschbach human patient study, three articles by Dr. Essers published between 1973 and 1975 show that use of EPO-rich human plasma (a pharmaceutical composition with a pharmaceutically-acceptable diluent or carrier) in humans caused a measurable reticulocyte response, evidencing the stimulation of erythropoiesis by human EPO (i.e. therapeutic effectiveness). (Spinowitz 752:15-762:22; TRX 2051, 2052, 2053). The only contrary testimony came from Dr. Friedman, who testified that the Essers studies did not show an increase in

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[13] The jury also heard evidence of another Eschbach study, in which the treatment of sheep with the EPO-rich plasma of other sheep was observed to "completely correct[] the anemia" and that therefore EPO therapy "should be effective in treating the anemia of chronic renal failure in humans." (TRX 2032; Spinowitz 749:15-750:24). While this reference is not anticipatory with respect to human EPO, it is powerful evidence of obviousness, and Dr. Spinowitz testified that claim 1 was in indeed obvious in light of this reference. (Spinowitz 751:17-20).

[14] Moreover, as explained above, because the EPO used in Dr. Eschbach's study cannot be shown to be structurally distinct from the recombinant EPO claimed in '933 claims 3, 7 and 8, a reasonable jury would could only conclude that Dr. Eschbach's study anticipates claims 3, 7 and 8.

hematocrit or that there was a change in the "clinical outcome of her patients." (Friedman 1496:14-24). This "evidence" ignores the fact that neither claims 9 or 12 of the '933 patent require an increase in hematocrit or beneficial "clinical outcome." It remains unrefuted that these studies resulted in an increased reticulocyte response from administration to humans of a pharmaceutical composition containing EPO that is structural identical to Amgen's recombinant EPO. Thus, a reasonable jury could only conclude that the Essers studies anticipate '933 claims 9 and 12.[15]

4. Miyake et al. (1977) Publication

Dr. Bertozzi also explained that the Miyake et al. (1977) article describing a purification method for erythropoietin from human urine discloses a pharmaceutical composition comprising a therapeutically effective amount of human EPO and a pharmaceutically acceptable diluent -- salt water. (Bertozzi 1006:3-1007:15, 1053:5-12; TRX 2002). Accordingly, based on this paper, a reasonable jury would have to conclude that claims 9 and 12 of the '933 patent are invalid for anticipation.[16]

IV. THE ONLY CONCLUSION THAT A REASONABLE JURY COULD REACH IS THAT THE ASSERTED CLAIMS OF THE PATENTS-IN-SUIT ARE OBVIOUS UNDER 35 U.S.C. § 103

A. Obviousness Under 35 U.S.C. § 103

Roche has presented clear and convincing evidence, which was unrefuted by any competent Amgen evidence, such that a reasonable jury would have to find the asserted claims invalid for obviousness. Under 35 U.S.C. § 103, "[a] claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at

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[15] Moreover, as explained above, because the EPO used in Dr. Essers' studies cannot be shown to be structurally distinct from the recombinant EPO claimed in '933 claims 3, 7 and 8, a reasonable jury would could only conclude that Dr. Essers' studies anticipate claims 3, 7 and 8.

[16] Moreover, as explained above, because the EPO described in the Miyake/Goldwasser paper cannot be shown to be structurally distinct from the recombinant EPO claimed in '933 claims 3, 7 and 8, a reasonable jury would could only conclude that this paper anticipates claims 3, 7 and 8.

the time the invention was made to a person having ordinary skill in the pertinent art." *In re Kahn,* 441 F.3d at 985; (*see also* D.N. 1141-4). Motivation to combine prior art references for purposes of § 103 "need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *See Dystar Textilfarben GmbH & Co. Deutschland KB v. C.H. Patrick Co.,* 464 F.3d 1356, 1361 (Fed. Cir. 2006). As the Supreme Court has recently held in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1742 (2007):

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp .... any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.[17]

B. Dr. Goldwasser's Purified Human Erythropoietin Renders Each of the Claims-In-Suit Obvious Pursuant to §§ 102(f)/103[18]

Dr. Goldwasser's transfer of purified human EPO to Amgen, including tryptic fragments created from this purified material, constitutes subject matter derived from another pursuant to § 102(f) which, in combination with other prior art, renders the asserted claims obvious to one of ordinary skill in the art. The Federal Circuit has held that "subject matter derived from another not only is itself unpatentable to the party who derived it under § 102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable ... under a combination of §§ 102(f) and 103." *OddzOn Prods., Inc. v. Just Toys, Inc.,* 122 F.3d 1396, 1403-04 (Fed. Cir. 1997); *see also Gambro Lundia AB v. Baxter Healthcare Corp*., 110 F.3d 1573, 1576 (Fed. Cir. 1997) (another person need only invent *part* of the invention to qualify under § 102(f)). Prior art pursuant to §

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[17] Additionally, for purposes of determining whether it would be obvious to combine elements into a claim, a "person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.*

[18] *See also* D.N. 1148.

102(f) "does not pertain only to public knowledge, but also applies to private communications between the inventor and another which may never become public." *OddzOn*, 122 F.3d at 1401-02.

The evidence pertaining to Dr. Goldwasser's contribution to the patents-in-suit remains undisputed. Prior to 1977, Dr. Goldwasser received a large supply of human urine concentrates containing EPO from Dr. Miyake. (TRX 2002). Prior to receiving this supply of human EPO, Dr. Goldwasser had been unable to obtain enough human EPO from other sources. (GW 522:23-25).[19] Drs. Goldwasser and Miyake then developed, under government grants from the National Institute of Health ("NIH") and the Department of Energy, a purification technique to obtain approximately 8 mg of pure human EPO. (GW 484:1-485:10, 526:10-13). Dr. Goldwasser made only very small amounts of this pure EPO available to parties other than Amgen and solely to perform radioimmunoassays ("RIA"). (GW 527:1-3). Dr. Goldwasser testified that he did not make amounts of protein sufficient for sequencing available to anyone other than Amgen. (GW 527:4-11). Indeed, Dr. Goldwasser testified that the amount of EPO needed for RIA was much smaller than that needed for sequencing and that, while crude EPO could be used for RIA, pure EPO was absolutely necessary for sequencing. (GW 527:18-20, 598:12–601:10, 604:10–605:2, 640:8-23). In fact, Dr. Goldwasser chose not to make sufficient amounts of pure EPO available to competitors of Amgen for sequencing because he knew it could result in someone other than Amgen cloning the EPO gene first and Amgen expressly ordered him not to provide such information to others. (GW 544:5-545:5, 538:23-25, 522:9-1, 546:18-21, 560:14-21; TRX 2038, 2044)

The evidence shows that once one of ordinary skill had Dr. Goldwasser's pure EPO protein, cloning the EPO gene would have been obvious. (Lowe 206:23-207:19, GW 531:5-17, 531:24-532:7, 639:11-20). Dr. Goldwasser testified that he conducted all of the work disclosed in Example

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[19] "GW" refers to the trial testimony of Dr. Goldwasser.

1, Table 1 of the patents in suit, including isolating the human EPO from urine and subjecting it to digestion with trypsin, resulting in the development and isolation of 17 discrete tryptic fragments. (GW 486:22-487:7, 486:9-21, 539:22-540:8, 613:2-9).[20] Moreover, Dr. Goldwasser testified that without his pure protein, Amgen could not have obtained the DNA sequence encoding human EPO. (GW 539:17-19). Amgen admits that Goldwasser's pure EPO was "critical to [its] program and eventual use of EPO as a therapeutic." (TRX 2041). Further, in the period from 1980-1983, Dr. Goldwasser was the sole source of significant amounts of purified EPO.[21] (GW 485:12-15, 485:22-486:2, 526:20-22; Lowe 179:1-4).

None of this clear and convincing evidence was refuted by Amgen's witnesses. Dr. Orkin's testimony about his own failures in isolating and cloning the EPO gene is entirely consistent with the critical nature of Dr. Goldwasser's contribution to the claimed "inventions." Dr. Orkin admitted that, unlike Amgen, he did not receive the tryptic fragments from Dr. Goldwasser, and he had "no erythropoietin in [his] hands that [he] sequenced." (Orkin 1603:20-1604:1). Moreover, in reporting to the NIH in 1983 on the progress of his own government-funded research on EPO, long before being retained as an expert in this case, Dr. Orkin, who considers himself to be "highly skilled in the art," stated "[t]he *most likely explanatio*n [for his failure to sequence the gene] is that the portion of the amino acid sequence used to construct the oligonucleotide probes, the C-terminal end of the 28 residue sequence is incorrect." (Orkin 1604:2-1607:20, 1653:1-6; TRX 2097 at AM-ITC 00260546). Had Dr. Orkin been fortunate enough to have Dr. Goldwasser's fragments, like Amgen did, he would not have faced this hurdle. Moreover, in a prior deposition Dr. Orkin testified under oath that he "stood ready to reactivate the [EPO] project at any time should there be more sequence

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[20] Amgen expressly relied on Example 1 to support its claims to human erythropoietin. (TRX 2009.554).

[21] Dr. Goldwasser defined pure EPO to mean that it has no discernible non-EPO present. (GW 525:14-16).

available," the very sequence that only Amgen had from Dr. Goldwasser. (Orkin 1649:14-24, 1651:2-16). Finally, when Dr. Orkin tried to suggest that one of skill in the art essentially had Dr. Goldwasser's protein from when he presented only a partial sequence at a 1981 presentation, Dr. Orkin admitted that this portion of the sequence was "highly degenerate." (Orkin 1667:10-24). He further admitted that "one of ordinary skill in the art would have been very discouraged by the high degree of codon degeneracy reflected by the identified amino acids." (Orkin 1669:22-1670:4; *see also* Hood 1990:12-14). Similarly, Dr. Lin, the sole inventor, admitted that Dr. Goldwasser's EPO protein was "critical" and that early problems in sequencing could be attributed to not having enough of the EPO protein. (Lin 1811:14-1812:8, 1815:5-16; TRX 2041, 2042).

1. The Skilled Worker Could Have Synthesized An EPO Gene Using Goldwasser's Purified Protein Rendering the Claims Obvious[22]

Before Dr. Lin had cloned the EPO gene, many other scientists were also working to make recombinant EPO, "because there was an apparent and obvious need to have sufficient human EPO to treat patients that had anemias, that had low blood counts for a variety of reasons, including kidney failure and cancer treatments." (Lowe 184:17-23, 186:18-25). Given the crucial tool, a sufficient amount of purified EPO to sequence, the prior art taught a predictable step-by-step solution using synthetic methods. (Lowe 205:17–207:12; *see also* Lowe 369:7-12). Indeed, "the most logical, straightforward way [to get the EPO gene], was to have the protein sequence of EPO" and then synthesize the gene using chemical methods available in the prior art. (Lowe 188:11-23; *see also* Lowe 178:11-18, 257:12-14).

By 1983, routine techniques were available to obtain accurate protein sequence from sufficient amounts of protein, including the use of a commercially-available machine for

[22] Amgen has, in the past, argued that Roche is required to show that the prior art must disclose the specific DNA structure of the EPO gene for the claims-in-suit to be rendered obvious. Amgen's position is untenable, as Roche explained in D.N. 1142, and Roche incorporates those arguments by references.

"microsequencing." (Lowe 217:23–218:11; TRX 2010). Indeed, Dr. Goldwasser admitted that if someone had Dr. Hood's gas-phase microsequencer, which Amgen did, they could have synthesized the tryptic fragments of EPO. (GW 531:5-532:5; *see also* Lin 1829:3-1830:7, 1839:20-24). Dr. Browne testified that this work would have been routine. (Browne 1992:11-14). Dr. Lowe stated that using a protein sequence and the standard codon table, one of skill in the art would have known to "work backwards" to obtain a corresponding DNA sequence encoding the protein. (Lowe 177:1-178:22, 206:2-207:11).

The Lin specification expressly states that when the complete protein sequence is known, the "method of choice" is the manufacture of synthetic DNA, as disclosed in the Alton WO 83/04053 application. (TRX 2 cols. 3:22-47, 30:48-63, 37:11-19; TRX 2034; *see also* Lowe 228:19-22). Admissions in a patent specification are binding on the patentee. *PharmaStem Therapeutics, Inc. v. Viacell, Inc*., 491 F.3d 1342, 1362 (Fed. Cir. 2007). Moreover, the prior art demonstrates that it would have been obvious to make a synthetic gene, including a January 1979 Goeddel article which reports expression of "chemically synthesized genes that encode the two chains of human insulin" and a 1977 Itakura article describing expression of a synthetic recombinant human somatostatin gene. (Lowe 229:20-25; TRX 2019; Lowe 169:20-22).

Amgen presented no evidence to counter the clear conclusion that gene synthesis would have been an obvious approach with a reasonable expectation of success. Indeed, even the Patent Office agreed that protein sequencing was non-inventive. (Lowe 225:20-24; TRX 2011.455). Accordingly, based on this method alone, obtaining the EPO gene would have been obvious in 1983-84, and no reasonable jury could conclude otherwise. Even if this technique was not obvious, however, multiple other obvious techniques were available.

2. Other Available Techniques Render The Cloning Of the EPO Gene Obvious

a. cDNA Cloning

As Dr. Lowe explained, in 1983, techniques for cDNA cloning had been described in a "widely known" 1982 treatise by Dr. Maniatis which, "akin to a cookbook," taught one of skill in the art "recipes" for isolating and cloning DNA sequences. (Lowe 164:15-25, 167:16-168:12). Using this technology, genes encoding several clinically useful proteins had been synthesized or cloned prior to the work by Amgen. (Lowe 168:20-175:3, 238:15-239:4, 241:4-17, 256:20-257:5; TRX 2021). Dr. Lowe explained that a 1981 article by Suggs describes how scientists used the sequence of the beta-2 microglobulin protein to work backward with the codon table to design DNA "probes." (Lowe 238:15-25; TRX 2021). These probes could then be used to screen and clone the DNA from a cDNA library. (Lowe 238:25-239:4). All of this work is cited to and summarized in the Maniatis manual. (Lowe 241:4-17).

In the face of the clear and convincing evidence and testimony presented by Dr. Lowe, Dr. Orkin attempted to postulate numerous difficulties one could encounter in cDNA cloning, suggesting this was not an obvious approach. However, all of Dr. Orkin's testimony as to the uncertainties one would have faced is contradicted by his own grant applications at the time.[23]

Dr. Orkin noted that the Maniatis manual states in its preface that "[a]lthough molecular cloning seems straightforward on paper, it is more difficult to put into practice." (Orkin 1597:10-15). However, Dr. Orkin failed to inform the jury that just a few lines later, it states: "To deal with these problems, a well-founded understanding of the principles underlying each procedure is essential. *We have therefore provided background information and references that may be useful should trouble occur*." (TRX 10 (emphasis added)). In other words, a primary purpose of Dr. Maniatis' treatise was to address the alleged "difficulties" set forth by Dr. Orkin. Accordingly, the

[23] Moreover, Dr. Orkin's opinions are limited up to the end of 1983 and cannot fully account for the obviousness or non-obviousness of cDNA cloning. (Orkin 1603:10-15). Accordingly, even if fully believed, Dr. Orkin's opinions cannot defeat the obviousness of cDNA cloning as of November 30, 1984.

documentary evidence itself defeats Dr. Orkin's baseless testimony. Moreover, Dr. Orkin testified that "cDNA cloning ... seemed to be the most likely to succeed," refuting any suggestion that a person of skill in the art would not have a reasonable expectation of success in using this technique. (Orkin 1579:20-21). Dr. Lin gave similar testimony. (Lin 1692:11-13, 1692:24-25).

Dr. Orkin argued that scientists at the time did not know for sure of a source of erythropoietin mRNA, a prerequisite for cDNA cloning. (Orkin 1566:6-8). However, Amgen's own patent specification, which constitutes a binding admission, admits that the 1983 Farber article "held that the results confirm the human kidney as a site of erythropoietin expression, allowing for the construction of an enriched human kidney cDNA library from which the desired gene might be isolated." (TRX 1 at col. 9:49-63; Lowe 247:20-24; TRX 2023). The prior art, including the Maniatis manual, taught how to make and screen cDNA libraries for cloning rare mRNAs. (TRX 10, 2022; Lowe 241:15-242:12, 244:13-20; Orkin 1618:7-9). Moreover, as Dr. Orkin admitted and the grant applications confirmed, he had a reasonable expectation that kidney tissue could serve as a source of EPO mRNA for cDNA cloning. (Orkin 1615:13-1616:9, *see also* Orkin 1565:12-14). Similarly, while Dr. Hood attempted to explain that cDNA would be difficult and "unlikely to work" for genes that are present in low abundance, Dr. Hood admitted that this was only as of 1980-81, before the Maniatis book was published. (Hood 1988:16-20).

Furthermore, Dr. Orkin admitted that once a cDNA library was constructed, which was a straightforward technique, (Orkin 1618:8-21), the "screening process is not the most labor-intensive." (TRX 2097 at AM-ITC 00260540; Orkin 1608:8-15). Dr. Orkin also told the NIH in 1980 that because of the smaller nature of the EPO protein sequence, "we can expect to reverse transcribe the entire mRNA into cDNA and obtain a complete copy of the erythropoietin sequence." (Orkin 1611:4-1614:8). This reasonable expectation is all that is required to support obviousness. Indeed, Dr. Orkin admitted that even when one had a partial peptide sequence, he was able, in 1983,

to isolate the full-length cDNA for phosphoglycerate kinase, providing the reasonable expectation of being able to do the same with a partial sequence of EPO. (Orkin 1620:12-1621:16; TRX 2099). With a partial sequence (which Dr. Lin had from Dr. Goldwasser), one of ordinary skill would have understood how to make probes based on the less degenerate portions to isolate the correct cDNA from a cDNA library. (TRX 2099; Orkin 1622:13-1623:14).

Obviousness does not require certainty; all it requires is a reasonable expectation of success. Amgen's own expert admitted that all the steps involved were well known and reasonably expected to lead to the cloning of the EPO gene in 1983. Accordingly, the evidence clearly and convincingly shows that cDNA cloning would have been obvious to a person of ordinary skill in the art.

b. Genomic Cloning

In 1983-84, it also would have been obvious to use a genomic library to clone the EPO gene. (Lowe 255:19–258:12). For example, a genomic DNA library named after Dr. Maniatis was publicly available and had been widely distributed. (Lowe 256:3-19). Examples of using a genomic library to isolate and clone genes, including the human beta-globin gene and human antibody genes, had been published. (Lowe 256:20–257:5).

Amgen attempted to defeat Roche's clear and convincing evidence by having Dr. Lin discuss all the difficulties he encountered in trying to isolate and clone the EPO gene using genomic cloning. However, as Dr. Lin acknowledged, none of the claims-in-suit are directed to genomic cloning. (Lin 1804:14-1809:18). Thus, even if genomic cloning was not obvious in light of the prior art -- which it is -- this does not defeat the clear and convincing evidence of obviousness of using other methods to obtain a DNA sequence encoding human EPO, discussed above, that one could use to carry out all the asserted claims by expressing such a DNA blueprint in CHO cells.

By Dr. Lin's own admission, none of the alleged difficulties discussed would have constituted a serious obstacle to one of skill in the art as solving these problems simply required the

application of well-known and routine techniques. Dr. Lin admitted that after he received the sequencing reports from Dr. Lai (which was obvious and routine, as discussed above), it took him an hour to design the probes. (Lin 1825:15-1826:7). Moreover, Dr. Lin admitted that using multiple probes or using fully degenerate probes was not novel. (Lin 1832:6-1834:10). Furthermore, hybridization techniques (to match the probe to the genomic library) were not novel and Dr. Lin simply followed the teachings of the prior art Woo publication. (Lin 1835:10-1836:6). Moreover, while Dr. Lin attempted to explained on direct examination that there were numerous difficulties in finding the optimal conditions for hybridization, he admitted on cross examination that Dr. Itakura had published an article in 1979 explaining how to optimize the conditions for hybridization, eliminating many of the difficulties postulated by Amgen. (Lin 1863:25-1865:12). There was nothing inventive in this technique. Furthermore, Dr. Lin did not invent the genomic library. This was a public library provided by Dr. Maniatis. (Lin 1836:7-1839:13; TRX 2101). After using all these well-known and non-inventive techniques, Dr. Lin was able to isolate the EPO gene. Indeed, Dr. Lin admitted that prior to his work, others in the prior art had used genomic cloning to isolate genes because they had the specific oligonucleotide sequence for the protein (which, in this case, Dr. Goldwasser only provided to Amgen). (Lin 1866:20-1867:6).

Accordingly, Amgen presented no evidence to rebut the clear and convincing evidence that genomic cloning is but one of multiple obvious methods to isolate and clone the EPO gene with sufficient amounts of the protein, which was provided only to Amgen.[24]

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[24] A reasonable jury would also conclude that the contemporaneous work of Dr. Fritsch further confirms the obviousness of Lin's DNA blueprint. The Federal Circuit has held that evidence of contemporaneous invention is relevant to the obviousness inquiry. *See Ecolochem v. S. California Edison Co.*, 277 F.3d 1361, 1379 (Fed. Cir. 2000) ("fact of near-simultaneous invention...is strong evidence of what constitutes the level of ordinary skill in the art."). Dr. Fritsch testified that he got the first shipment of EPO from Dr. Miyake in April 1984. (Fritsch 350:21-351:8). As Dr. Lowe explained, based on his review of the evidence, once Genetics Institute had the protein, it took

(continued...)

3. Expressing The EPO Gene To Make An In Vivo Biologically Active Protein and Pharmaceutical Composition Was Obvious

Once one of ordinary skill in the art has the DNA blueprint, it would be obvious by 1984 to use vertebrate cells, which include mammalian cells such as CHO cells, to recombinantly produce a human glycoprotein, such as EPO. The evidence shows that all of this work at Amgen was done by persons of ordinary (or less) skill in the art other than Dr. Lin, without direction from Dr. Lin. Accordingly, a reasonable jury could be led to only one conclusion: that these subsequent steps were routine and obvious and required no inventive contribution.

Amgen scientist Dr. Browne began working at Amgen before even earning a graduate degree, (Browne 1910:12-1911:11). His primary responsibility soon thereafter was to express the cloned EPO gene in mammalian cells to produce the EPO protein. (Browne 1911:14-16, 1931:14-19). Dr. Lin admitted that it was Dr. Browne, a non-inventor, who took the DNA and chose what expression vector to use. (Lin 1841:8-1842:23). Dr. Lin explained that he did not need to instruct Dr. Browne -- any scientist would know how to carry out this process. (Lin 1845:17-20).

Dr. Lowe's unrefuted testimony established that the prior art was replete with examples of using mammalian and CHO host cells to recombinantly produce proteins, including human interferon and human interleukin-2. (*See* Lowe 171:8-172:14, 181:23-182:4, 267:11-16, 272:21-273:16, 275:22-276:4, 281:11-16, 287:21-24, 291:3-5, 306:2-12; TRX 10, 2024, 2026-30). CHO cells were widely available from the ATCC, "a publicly accessible cell repository." (Lowe 176:8-14). Dr. Lin admitted that he got the idea to use CHO cells from the ATCC and that it was known to use mammalian cells because they produce sugared proteins. (Lin 1854:7-1857:5). Amgen did not refute that it was obvious to grow such host cells under suitable nutrient conditions. (Lowe

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"[a]bout six to eight weeks" to actually clone the gene. (Lowe 467:25-468:2). This contemporaneous evidence further supports the conclusion that cloning the gene was obvious if one had enough protein.

182:11-14, 182:21-24, 291:3-11, 304:10-14, 306:2-12). Indeed, this step was independently carried out by Dr. Browne, a non-inventor, shortly after he earned his graduate degree and had not yet obtained the requisite experience of a person of skill in the art at the time of the invention. (Browne 1937:14-17). One of ordinary skill would also have known how to perform a radioimmunoassay,[25] which, as Dr. Lowe testified and Dr. Lin admitted, is a "standard laboratory technique." (Lowe 304:20-25; Lin 1846:11-20). Moreover, certain non-human transcription control sequences were well-known in the art, and it would have been obvious to use one to control transcription of the EPO gene. (Lowe 305:1-9, 306:1-12). For example, the SV40 viral promoter sequence was a "standard control sequence in wide use at this time." (*Id.*; TRX 2030).

Dr. Lowe explained that "[i]t would be ... straightforward to install the blueprint ... into the cell, and the cell would, by virtue of its inherent abilities, take that blueprint and turn it into ... the product that the blueprint was instructing the cell to do." (Lowe 173:23-174:8, 182:25-183:18, 201:17-25; TRX 10). Accordingly, "the cell will carry out its inherent function ... and be instructed by that ... gene to make" the protein, as exemplified by the prior art describing expression of glycoproteins in mammalian cells that Dr. Lowe discussed. (Lowe 174:15-18). Amgen did not refute that by 1984, it was well-known that the cell acts like a factory and carries out its normal function to produce a glycosylated protein. (Lowe 172:15-173:10, 181:4-10, 182:2-4; Bertozzi 1016:16-21 *see also* TRX 2012.675-76). As Dr. Lin admitted, he chose mammalian cells because it was well-known that mammalian cells "can put sugars onto the protein." (Lin 1754:4; *see also* Lin 1848:17-22). Similarly, Dr. Browne testified that three months after first attempting to express EPO in 293 cells, he succeeded, and he could not say that this work required any inventive skill. (Browne 1975:20-22, 1976:6-17).

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[25] As explained by Dr. Flavell, this technique cannot measure human EPO as claimed.

Moreover, Dr. Lowe explained that "gene amplification" was a widely-known technique for making the "cell factory" more effective in making its proteins. (Lowe 267:18-24, 268:9-12; 306:1-12). Dr. Lowe testified that these methods were well-known by 1984, and were taught in the Axel patent (TRX 2024) and the Kaufman and Sharp paper. (Lowe 269:19-21; TRX 2025). Similarly, the use of an amplified marker, such as dihydrofolate reductase ("DHFR"), was well-known. (Lowe 283:24-284:3; TRX 2029; *see also* Lowe 287:17-288:4, 293:1-8). This evidence was unrefuted by Amgen, as Dr. Lin confirmed that gene amplification using DHFR as a selectable marker was well-known at the time. (Lin 1859:3-12).

While Dr. Lin suggested that his choice of CHO cells among *two choices* suggested by the ATCC was somehow inventive, such an argument has no basis in view of the substantial prior art pointing to CHO cells as an obvious choice for commercial production of a human glycoprotein and the clear standards for obviousness provided by *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727. (*See* TRX 2026-29).

Before Dr. Lin's "invention," the prior art provided more than a reasonable expectation that the protein expressed by the host cell would have *in vivo* biological activity, which for EPO includes increased production of reticulocytes and red blood cells. (Lowe 181:13-19, 170:19-22, 169:20-22, 169:23-170:5, 170:9-10, 247:25–248:22, 251:15-19, 275:22-276:4, 281:11-16; Harlow 1785:5-9, 1786:21-1787:8; *see also* Claim Construction Order, D.N. 613; TRX 2023, 2026-30). Before Dr. Lin did any testing to determine the biological activity of EPO, he had an expectation of *in vivo* biological activity. (Lowe 261:9-13; 276:23-277:22, 288:22-289:2; TRX 2014 at RO008891370-75 (claiming *in vivo* biologically active EPO (claims 1, 6 and 9) and a process for making it (claim 27))). As Dr. Lin agreed, this expectation was "more than just a guess" (Lin 1880:9-12), and is further confirmed by the fact that Dr. Lin admitted he claimed an *in vivo*

biologically active protein before ever producing an active protein in a host cell. (Lin 1884:13-22). Dr. Lin's expectation of success is consistent with the prior art. (Lowe 207:12–208:5, 277:23-25).

By 1984, isolating a glycosylated protein from nutrient media was widely known and involved centrifuging the nutrient media to separate protein from debris and other cells. (Lowe 183:19-184:3, 207:22-208:22). This testimony went unrefuted by Amgen.

Once one of ordinary skill isolated the glycoprotein from the host cell, it would have been obvious to prepare a therapeutically effective pharmaceutical composition comprising the glycoprotein and a pharmaceutically-acceptable diluent, adjuvant or carrier. As explained above, numerous studies not only render claims to pharmaceutical compositions obvious, they actually anticipate these claims. *See Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998) ("anticipation is the epitome of obviousness"). Prior to the filing of the Lin patents, human erythropoietin was demonstrated to be a pharmaceutical composition containing a diluent, adjuvant, or carrier that was therapeutically effective. (Spinowitz 711:9-17, 720:7-14, 742:22-743:9; Bertozzi 1006:8-1007:15, 1009:13-1012:14, TRX 2002, 2004, 2032, 2043, 2045, 2049-53). Dr. Spinowitz provided many examples, including the Baron-Goldwasser clinical study, the 1984 Eschbach study and the Essers studies. Dr. Bertozzi also testified as to the administration of a pharmaceutical composition containing human EPO to mice described in the 1977 Miyake paper. (Bertozzi 1006:8-1007:15, 1009:13-1012:14; TRX 2002). These studies all used a pharmaceutical composition of human erythropoietin. (Spinowitz 695:19-696:1, 708:7-25, 743:1-9, 753:25-754:8; TRX 2004, 2051-53).

Similarly, "therapeutically effective" pharmaceutical compositions of erythropoietin were well-known in the art. Indeed, the same studies Drs. Spinowitz and Bertozzi discussed regarding

"pharmaceutical composition" also demonstrate therapeutic effectiveness.[26] Moreover, the same prior art taught using such pharmaceutical compositions to treat dialysis patients, including using the composition to raise hematocrit in patients. (Lowe 298:16-301:1; Spinowitz 764:14-23, 769:5-10, 771:23-25, 781:7-10, 782:11-18; TRX 2004, 2032, 2051-53; *see also* D.N. 1145). The 1984 Eschbach study administering EPO-rich sheep plasma to uremic sheep maintained on dialysis clearly and convincingly renders '933 claims 9, 11, 12 and 14 and '422 claim 1 invalid for obviousness when combined with other prior art. This paper, published in the Journal of Clinical Investigation (TRX 2032), teaches one of skill in the art to administer a pharmaceutical composition comprising erythropoietin to sheep in order to elicit an increase in hematocrit. (TRX 2032 at Figure 6; Spinowitz 782:11-18, 752:10-11). The Eschbach reference also expressly teaches that "[t]hese results predict that [EPO] therapy should be effective in treating the anemia of CRF in humans." (TRX 2032 at p. 435; Lowe 298:5-11; *see also* TRX 2033 (1971 Goldwasser article) ("Erythropoietin ... is important ... for possible therapeutic use in some types of refractory human anemias"); Bertozzi 1054:5-16). Accordingly, a person of ordinary skill in the art would read this prior art study as providing a reasonable expectation of success in administering a pharmaceutical composition of EPO to CRF patients to increase hematocrit.

Moreover, before Drs. Baron and Goldwasser submitted their IND to the United States Food and Drug Administration to obtain approval to conduct their clinical study, they administered the same pharmaceutical composition later used in the Baron-Goldwasser clinical study to hamsters for toxicology testing. (Spinowitz 769:22-770:1; *see generally* TRX 2004 at AM-ITC 01006680-752). As part of that study, the doctors measured the hematocrit of eight hamsters; four hamsters received

[26] *See* discussion *supra* pertaining to anticipation under § 102. (*See also* Spinowitz 711:3-17, 21-23; 712:2-12, 713:17-19, 719:7-13, 748:18-749:11, 752:19-753:6, 753:25-754:8, 759:8-17, 793:22-794:10; Bertozzi 1006:8-1007:15, 1009:13-1010:2, 1010:25-1011:10, 1011:21-1012:14; TRX 2002, 2004, 2032, 2045, 2049, 2051-53, 2054.2 at AM-ITC 00056316).

the Baron-Goldwasser pharmaceutical EPO composition and four hamsters served as controls. (Spinowitz 770:23-24; TRX 2004 at AM-ITC 01006680). When hematocrit was measured, those hamsters that received the erythropoietin therapy had a "much higher" hematocrit than the control hamsters. (Spinowitz 770:17-771:5; TRX 2004 at AM-ITC 01006695). This study further confirms that the Baron-Goldwasser pharmaceutical composition was capable of increasing hematocrit. (Spinowitz 771:23-25). The fact that the hamster and sheep experiments were not performed on humans is of no moment for obviousness purposes. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (tests on humans are not required to show predictable success in treating humans).

To the extent Amgen attempted to refute any of these clear conclusions, it was only in the realm of anticipation, not obviousness, and all of those attempts utterly failed, as explained above.

4. A Person Of Skill In The Art Would Be Motivated To Combine These Elements With A Reasonable Expectation Of Success

Motivation to combine can derive from various sources. Here, the academic and market pressures faced by skilled workers prior to 1984 provided such motivation. By 1984, scientists other than Dr. Lin were interested and working on cloning the EPO gene to put it in a host cell to make biologically active EPO and use that EPO as a composition to treat chronic renal failure in dialysis patients. (Lowe 184:17-21, 186:18-25). In view of this interest and need, the person of ordinary skill in the art would have been motivated to follow the well-established techniques recited in the claims-in-suit with a reasonable expectation of success, save for the fact that no one other than Dr. Lin could get sufficient amounts of EPO for cloning and sequencing. Accordingly, as Roche's witnesses explained, a reasonable jury could conclude that all of the claims-in-suit are invalid for obviousness. *See* D.N. 1141-3.

C. Amgen Presented No Pertinent Evidence of Secondary Considerations

The only evidence Amgen has put forth to overcome Roche's clear and convincing evidence of *prima facie* obviousness is that there was a long felt need for an anemia treatment for chronic

renal failure patients and a failure of others to achieve that particular goal. As the discussion above clearly indicates, any long felt need was for *EPO therapy* for renal anemia patients. The testimony of those of skill in the art and the prior art, discussed above, confirms the widespread understanding in 1983-84 that treatment with EPO *would* meet this long felt need. Also as discussed above, routes to obtaining EPO in the large quantities necessary for widespread therapy were obvious once a source of the protein was secured. Therefore, the evidence that Amgen's relies as secondary indicia of obviousness are at once misplaced and irrelevant.

Amgen presented "evidence" of a purported long-felt need through the testimony of Ms. Spaeth and Dr. Friedman.[27] However, Amgen never came close to establishing that there is a sufficient nexus between Amgen's commercial product Epogen® and the disclosure supporting the claimed invention of the patents-in-suit. As noted earlier, the law is clear that such a showing is required, and Amgen has the burden of proof. Amgen has not, and cannot, make this required showing. Amgen maintains that Example 10 of the common specification embraces Epogen®, but the evidence clearly shows otherwise. Dr. Browne admitted that Example 10 plainly states that the cell culture media in the example are a "genetically heterogenous population" of cells. (Browne 1982:17-22; TRX 1, col. 26:66-67). Amgen could not prove that the population was homogenous. (Browne 1983:10:20). The FDA, however, requires a homogenous population and, eventually -- after the Lin specification was filed -- Amgen was able to create a homogenous population (i.e. multiple cells all derived from one cell) to obtain FDA approval for Epogen®. (Browne 1983:10-15).

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[27] Ms. Spaeth testified, however, that she chose to discontinue taking Epogen® in favor of Aranesp® (Spaeth 1534:18-1535:2), a product that Amgen admits is not covered by any of the asserted claims.

Moreover, Amgen's scientist Dr. Strickland admitted that Epogen® is purified by a method that he invented after the November 1984 filing date of the patents-in-suit. (Strickland 2148:15-2151:25; TRX 2011.201). These purification methods were not available in 1984 and because the purification technique used necessarily affects the final EPO product, any success of Epogen® cannot be tied to the patents-in-suit. As shown in Dr. Strickland's '298 patent (TRX 2104), different purification techniques select different isoforms of human EPO produced in CHO cells and result in a different final product with different specific activity. (Strickland 2157:12-2165:4; TRX 2104). Accordingly, Amgen cannot show the requisite nexus between Example 10 and Epogen®, which at best is a product with merely a portion of the isoforms that may be produced by the heterogeneous collection of cells in Example 10. In sum, the evidence is clear and unrefuted that, as Drs. Browne and Strickland admitted, Example 10 does not embrace what eventually became Amgen's commercial product, and therefore did not satisfy any long felt need for anemia therapy.[28]

Even if Example 10 disclosed enough information to embrace Amgen's commercial product, Amgen's expired '008 patent shares a common specification with all the patents-in-suit and was the only of Amgen's patents to be in force when Epogen® was FDA approved and marketed in 1989. (Browne 1955:19-22). Indeed, the patents-in-suit did not issue until 1995, yet Epogen® enjoyed commercial success well prior to issuance of the patents. Accordingly, even if a nexus for secondary considerations could be shown, it would only pertain to the '008 patent and not the patents-in-suit. There is ample law supporting such a conclusion. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (secondary considerations were "not significantly probative of" non-obviousness where the patentee had the right to exclude others from

[28] Because Amgen has not come close to showing the requisite nexus, the testimony of Dr. Friedman and Ms. Spaeth is wholly irrelevant.

practicing the method specified in the patent-at-issue by virtue of another patent); *Weatherchem Corp. v. J.L. Clark, Inc.*, 163 F.3d 1326, 1335 (Fed. Cir. 1998) (commercial success of a product was attributable mostly to a prior patent).

Finally, the only evidence of failure of others was presented through Dr. Orkin, who discussed his own difficulties in trying to isolate and clone the EPO gene. As the evidence makes entirely clear, the only reason Dr. Orkin failed was because he, unlike Amgen, did not have Dr. Goldwasser's protein. Accordingly, Dr. Orkin's failures do nothing to overcome the clear and convincing evidence of obviousness of the claims-in-suit.

V. A REASONABLE JURY WOULD FIND THAT THE ASSERTED CLAIMS OF AMGEN'S PATENTS ARE OBVIOUS PURSUANT TO § 102(g) AND § 103

A. § 102(g)(2) Art Combined with the Prior Art Can Render Claimed Inventions Obvious Pursuant to § 103

Pursuant to 35 U.S.C. § 102(g)(2), "[a] person shall be entitled to a patent unless ... another inventor ... establishes ... that before such person's invention ... the invention was made in this country by such other inventor who had not abandoned, suppressed or concealed it." Courts have made clear that § 102(g)(2) does not require knowledge or use of a prior invention that was publicly accessible at the time the patented invention was made. *See E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.3d 1430, 1437 (Fed. Cir. 1988) ("certain prior work at issue, solely because it satisfied § 102(g) (*i.e.* it was reduced to practice and had not been abandoned, suppressed or concealed), could be used for § 103 purposes"); *see also* D.N. 1141-5.

B. Dr. Goldwasser's Tryptic Fragments Are Section 102(g)(2) Prior Art And Render The Claims-In-Suit Obvious

Dr. Goldwasser's tryptic fragments also invalidate the claims-in-suit under §§102(g)/103. As noted, Dr. Goldwasser did all the work with respect to tryptic digestion as referred to in Table 1 of Example 1 of the patents-in-suit. (GW 568:12-13). There is no evidence that he abandoned, suppressed or concealed this information -- in fact, after he gave it to Amgen, making it sufficiently

"public" for purposes of § 102(g)(2), Goldwasser timely published this information in the Lai 1986 paper (TRX 2047). Accordingly, as explained above, Dr. Goldwasser's tryptic fragments, when combined with the prior art, render the claims-in-suit invalid for obviousness.

C. Dr. Fritsch's Prior Invention Constitutes Invalidating § 102(g) Prior Art

Dr. Edward Fritsch at Genetics Institute cloned an EPO cDNA, transfected it into COS and CHO cells, and expressed high levels of *in vitro* and *in vivo* biologically active human EPO. (*See* Frtisch 350:19-306:21; TRX 2084, 2090). All of this work was completed before November 30, 1984. Indeed, Amgen concedes that Dr. Fritsch cloned the EPO gene on August 20, 1984, and that he expressed EPO in CHO cells in September 1984 – both before Amgen's filing date. *See* D.N. 1031 at 2. As Amgen has failed to introduce evidence of an earlier invention date for any of the claimed subject matter, Dr. Fritsch's invention stands as prior art for all of the asserted claims.[29] Dr. Fritsch's invention, described in an article sent to the journal *Nature* in December 1984, and published in February 1985, was not abandoned, suppressed or concealed. (*See* TRX NJT); *see also Dow Chem. Co. v. Astro-Valcour, Inc*., 267 F.3d 1334 (Fed. Cir. 2001). Accordingly, there can be no dispute that Dr. Fritsch's invention stands as prior art under § 102(g), and thus it renders each of the asserted claims of the '422 and '933 patents invalid as anticipated and/or obvious.

VI. A REASONABLE JURY WOULD CONCLUDE THAT ROCHE PREVAILS ON ITS SECTION 112 DEFENSES

[29] Amgen has, in the past, asked this Court to take judicial notice of facts found by the Board of Patent Appeals and Interferences in the *Fritsch v. Lin* interferences (*see* D.N. 1031 at 2 n.10, 3 n.11); however, findings made by an administrative body cannot bind this Court Likewise, this Court should not take notice of the facts set forth in *Amgen Inc. v. Chugai Pharm. Co.*, 13 U.S.P.Q. 2d 1737 (D. Mass. 1989), because none of the asserted claims (nor any of the patents-in-suit) were involved in that proceeding, and because Roche was not a party. (*See also* D.N. 838).

A. A Reasonable Jury Would Find Claims to "Human Erythropoietin" Invalid For Lack Of Written Description and Indefiniteness

Roche has presented sufficient evidence such that a reasonable jury could only conclude that claims to "human erythropoietin," including claim 1 of the '422 patent, claims 1-2 of the '868 patent, claims 6-9 of the '698 patent, claim 7 of the '349 patent and claims 3, 7, 8, 9, 11, 12 and 14 of the '933 patent are invalid under Section 112 for lack of written description and/or indefiniteness.

Patent law requires that "the specification shall contain a written description of the invention." 35 U.S.C. § 112. The written description must show that the applicant was in full possession of the claimed subject matter on the application filing date so as to allow other inventors to develop and obtain patent protection for later improvements and subsequent inventions that build on the applicant's teachings. *TurboCare Div. of Demag Delavel Turbomachinery Corp. v. GE*, 264 F.3d 1111, 1118 (Fed. Cir. 2001); *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976). However, "[a]pplication of the written description requirement ... is not subsumed by the 'possession' inquiry. A showing of 'possession' is ancillary to the *statutory* mandate that '[t]he specification shall contain a written description of the invention,' and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 969 (Fed. Cir. 2002) (emphasis in original); *see also Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) ("invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*") (emphasis in original).

The adequacy of the written description (*i.e.*, the disclosure) is measured from the face of the application. *New Railhead Mfg. LLC v. Vermeer Mfg.*, 298 F.3d 1290, 1295 (Fed. Cir. 2002); *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 927 (Fed. Cir. 2004) ("[I]t is in the patent specification where the written description requirement must be met."). Importantly, the description of a single species within a claimed genus may not be sufficient to support patentability under § 112, ¶1. *Regents of Univ. of Cal. v. Eli Lilly & Co*, 119 F.3d 1559, 1567 (Fed. Cir. 1997).

Similarly, although a patent specification may render the claimed invention obvious, that disclosure "is not sufficient to satisfy the written description requirement of that invention." *Id.*; *see also Lockwood v. Am. Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification").

The asserted claims to "human erythropoietin" are invalid because that term, as it is defined by this Court, is not described in the patent. "Human erythropoietin" has been construed by the Court to mean "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." (Claim Construction Order, D.N. 613, at 15). Thus, the amino acid sequence of human EPO as "isolated from human urine" is cited as a specific example of "human erythropoietin." The distinguishing feature of this definition is the amino acid sequence. (Flavell 1216:7-16). In order to adequately describe "human erythropoietin" in light of this definition the patent must contain a description of the specific amino acid sequence of EPO isolated from human urine -- *i.e.* the +1 to +165 residues of human urinary EPO known today.

Dr. Flavell presented substantial evidence that '422 claim 1, '868 claims 1-2, '698 claims 6-9, '933 claims 9, 12 and 14 and '349 claim 7 are invalid for lack of written description as to the claim term "human erythropoietin."[30] Dr. Flavell testified that there are few descriptions of the human EPO amino acid sequence in Amgen's patents and none of them describe the specified example in the Court's definition of an amino acid sequence of EPO isolated from human urine. For example, the patent includes a depiction of an amino acid sequence in Figure 6. (TRX 1). The specification expressly states that Figure 6 "serves to identify the primary conformation (amino acid sequence) of mature EPO as including 166 specified amino acid residues." (TRX 1 col. 21:3-6;

[30] The '349 patent recites "erythropoietin" but Amgen has not contended that this claim is directed to anything other than human erythropoietin. Furthermore, Claim 7 is dependent on Claim 1 which recites "human erythropoietin." In fact, Amgen indicated in its Markman brief that "human erythropoietin" should apply to '349 Claim 7. Amgen, Inc.'s Response to Defendants' Claim Construction Brief (D.N. 323) at p. 5.

Flavell 1220:7-12). The Federal Circuit has cautioned that "the detailed description in the [Lin specification] indicates that the specificity of Figure 6 is not to be lightly disregarded." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d at 1343. According to Dr. Flavell, this figure depicts to one of skill in the art a human EPO gene encoding a pre-protein sequence which is cleaved by the cell to yield a protein having a sequence of 166 amino acids. (Flavell 1274:16-1275:14).

The patents also recite other amino acid sequences. One is an amino acid sequence of +2 to +166 and another is identified as an amino acid sequence of -1 to +166 (TRX 1, col. 32:17-24) -- both sequences are different from the 165 amino acid sequence of human urinary EPO and different from the 166 residues for mature human EPO set forth in Figure 6. The only 165 amino acid residue protein described in the Lin specification is monkey EPO (TRX 1, col. 19:42-47), which is a different product than what Amgen now claims. Monkey EPO is not human EPO, let alone EPO isolated from human urine. Moreover, Dr. Lodish testified that the amino acid sequence of human urinary EPO was not known when Dr. Lin filed his patent application and Table 1 sets forth only fragments of the amino acid sequence. (Lodish 2339:18-21; TRX 1, col. 15:29-60). Taken as a whole, the evidence is clear that there is no description of the amino acid sequence of EPO isolated from human urine in the common specification of the patents in suit. Therefore, claims incorporating the element "human erythropoietin" are invalid for lack of written description.

Dr. Flavell also explained that even though the Amgen patents purport to embrace multiple "polypeptides of the invention" and "allelic forms" of human EPO sequences, the patents only describe human EPO as the specific +1 to 166 amino acid sequence in Figure 6. (Flavell 1225:14-1226:6; TRX 1, col.35:15-20). There are potentially countless allelic forms of human EPO, none of which are identified or described in the specification. Nor does the specification describe the 165 amino acid sequence of human urinary EPO known *today*. (Flavell 1231:1-6; 1244:2-6). The patents would have to describe at least this much to describe human EPO pursuant to the Court's

definition. *See Vas-Cath Inc.*, 935 F.2d at 1563-64 ("invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*").

The evidence further shows that even after the effective filing dates of the patents, Amgen maintained that human EPO was a protein 166 amino acids in length. Dr. Flavell addressed a 1986 paper Amgen paper, authored by Por Lai, that depicted the sequence of human EPO as having an arginine at position 166. (TRX 2047; Flavell 1227:19-25). In Figure 4B-7 of its IND application for Epogen®, submitted to the FDA a year after the Lin application was filed with the PTO, Amgen also described human EPO as a protein having 166 amino acids. (TRX 2070). Additional articles, including the 1986 Browne paper and the 1985 Lin paper also confirm Amgen's continual understanding that human EPO was 166 amino acids. (TRX 2059 at Fig. 2; TRX 2096). For purposes of written description, claims to polypeptides encoded by particular DNA sequences are limited to the known polypeptide products of that DNA at the time of filing. *See Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1354 (Fed. Cir. 2000); *Chen v. Bouchard,* 347 F.3d 1299, 1305 (Fed. Cir. 2003) (finding that inherency will not support adequate written description where the procedures disclosed in the specification actually produce the structure expressly disclosed as well as the structure allegedly inherently disclosed).

Dr. Flavell explained that the assays described in Example 10 and elsewhere in the patent specification each fail to provide adequate description of EPO isolated from human urine sufficient to meet the requirements of the Court's claim construction. There is simply no evidence of the structure of the protein that results from carrying out Example 10, no evidence of its amino acid sequence, and more importantly, no evidence about how to obtain such information necessary for

adequate written description under 35 U.S.C. § 112, first paragraph.[31] (Flavell 1364:15-18; 1365:11-14). The written description requirement is not met "if one of ordinary skill in the art must first make the patented invention before he can ascertain the claimed features of that invention." *New Railhead*, 298 F.3d at 1295.

Based on the above evidence, Dr. Flavell concluded that the 165-amino acid protein exemplified in the Court's claim construction is not described in the patents. Dr. Flavell therefore concluded the patents fail to describe the full scope of polypeptides encompassed within "human erythropoietin," and that claims containing this term were invalid. Indeed, Amgen's expert, Dr. Lodish, admitted that Lin did not disclose that the 166 amino acid residue shown in Figure 6 of the specification may be removed, in some instances, to produce a protein of 165 amino acids. (Lodish 2340:21-24). Likewise, Dr. Lodish admitted that Dr. Lin never amended his specification to describe an EPO protein with the +1 to +165 amino acid sequence of human EPO as now claimed by Amgen. (Lodish 2340:14-25). Amgen also admitted in FDA filing in 1986 that the 165 amino acid sequence of Epogen® (which, as explained above, is not the product of example 10) was based on "newly acquired data" years after Lin's specification was filed. (TRX 2086 at AM-ITC00065045).

Section 112 also requires that the specification "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention". 35 U.S.C. §112. Simply put, section 112 requires that the claims of a patent must clearly inform those skilled in the art as to "what is claimed when the claim is read in light of the specification." *Morton Int'l. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993).

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[31] Amgen has previously noted that Dr. Lin mentions "human erythropoietin" in numerous places in the patent specification, particularly in Example 10. (D.N. 1137-2 at 39). However, merely mentioning human erythropoietin does not provide the necessary written description for the amino acid sequence of EPO isolated from human urine as required by the patent law. Furthermore, Example 10 does not include the amino acid sequence of *any* protein.

The claims-in-suit are indefinite based on the term "human erythropoietin." Dr. Flavell testified, and the patent states, the monkey and human EPO sequences listed in Figures 5 & 6 of the patent "do not limit the scope of useful polypeptides provided by the invention." (TRX 1 col.35:15-17). The patent specification, which is binding as an admission against Amgen, contemplates dozens of "polypeptides of the invention" that fall within the scope of "human erythropoietin," including mutants, analogs and allelic variants. The full scope of this class of polypeptides is hopelessly unclear. Therefore, based on the evidence, a reasonable jury must conclude that the amino acid sequence of the claim term human erythropoietin is indefinite.

B. A Reasonable Jury Would Find Claim 1 of the '422 Patent is Further Indefinite As Lacking Any Identifiable Structure

Indefiniteness arises when the claim language is "not sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton Int'l.*, 5 F.3d at 1470; *Semmler v. American Honda Motor Co.*, 990 F. Supp. 967, 975 (S.D. Ohio 1997). The number of structures encompassed within the term "human erythropoietin" renders '422 claim 1 indefinite because it leaves potential competitors with no idea as to whether or not they are infringing.

Drs. Bertozzi and Flavell testified that the term "human erythropoietin" as defined by the Court encompasses an endless possibility of structures that would not signal to one of skill in the art the boundaries of this claim element. (Bertozzi 1154:21-1155:9; Flavell 1244:14-1245:3). Dr. Bertozzi also stated that because the Court's definition of "human erythropoietin" is based solely on its amino acid sequence the term encompasses a limitless variety of proteins having different glycosylation patterns (or no glycosylation at all). (Bertozzi 1164:6-14). In fact, the patent says nothing about the actual structure of human EPO. (Bertozzi 1155:3-4).

Dr. Flavell similarly testified that the patent specification embraces an unspecified number of structures. The patent cites an unlimited number of "polypeptides of the invention" and "allelic forms" of human EPO that are potentially within the scope of the Court's claim construction.

(Flavell 1244:14-1255:11). This breadth makes it impossible for one of skill in the art to identify what was properly within the definition of "human erythropoietin."

Moreover, the knowledge of one of skill in the art concerning the "amino acid sequence of EPO isolated from human urine" would have changed from 1984 to today. Other proteins could be isolated from human urine in the future that would have an even different structure, and yet would fall within the Court's claim construction. Accordingly, the exemplar in the Court's claim construction is nothing more than a moving target that renders claims containing this term indefinite. *See Amgen, Inc.*, 126 F. Supp. 2d at 155.

Claim 1 of the '422 patent also recites erythropoietin "purified from mammalian cells in culture." (TRX 0005 at col.38 l.35-41). As discussed above, this term does not cure the indefiniteness of the claim because it does not change the fact that countless structures are covered. This Court has previously found that absent clear guidance on which human urinary EPO standard to use, 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 EPO because urinary preparations differ in their glycosylation. *Amgen, Inc.*, 126 F.Supp.2d at 156.

Dr. Bertozzi testified that erythropoietin glycoproteins made by recombinant mammalian cells and mammalian cells in culture have the same structures as those found in Goldwasser's prior art human urinary EPO. (Bertozzi 999:15-21, 1153:5-10). Indeed, Dr. Bertozzi testified that there is still "a huge universe of glycoforms" that can be produced from mammalian cells. (Bertozzi 1155:3-9). Thus, EPO "purified from mammalian cells" does not impart structure above and beyond that found in human urinary EPO. A claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations. *Amgen*, 314 F.3d at 1340. Therefore, the claim is still indefinite. Amgen's witness, Dr. Varki, provided no credible or relevant evidence in rebuttal, as previously explained.

In addition, as noted above, the term mammalian is a broad term that encompasses over 30,000 mammalian cells. (Bertozzi 1155:20-1156:2; Varki 2247:8-10). Purification adds a further level of indefiniteness because the glycoforms present at the end of a purification process can vary from batch to batch. (TRX 2057; Bertozzi 1164:18-1165:3). Along with the evidence described above, this language renders the '422 claim 1 indefinite.

C. A Reasonable Jury Would Find That '349 Claim 7 Is Invalid For Non-Enablement Regarding The Limitation to Radioimmunoassay (RIA)

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). Claim 7 of the '349 patent is a dependent claim that incorporates the limitation of host cells capable of producing a certain amount of erythropoietin in 48 hours "as determined by radioimmunoassay." (TRX 0004). Claim 7 of the '349 patent is not enabled. Furthermore, it is unclear that *any* amount of experimentation would enable the claim.

Dr. Flavell gave testimony that in his opinion and taking all the evidence into account claim 7 is not enabled. (Flavell 1255:18-21). He explained that radioimmunoassay (RIA) is an assay that involves the use of antibodies. (Flavell 1261:8-11, 1261:24-1262:3). The antibodies bind to small sites on a molecule known as epitopes. Dr. Flavell explained that the antibodies used in an RIA do not distinguish between human EPO and EPO fragments, but instead measure anything that contains a small binding site (called an epitope) that the antibody targets and binds. (Flavell 1264:21-1265:8, 1267:17-3).

Ample evidence has been presented that these fragments exist and will confound RIA results. By Dr. Goldwasser's own admission, EPO fragments not only exist, but can be measured in an RIA along with biologically active human EPO, resulting in an overestimation by RIA of the amount of biologically active EPO present. (TRX 2073). At a pre-IND meeting in 1985, Amgen

scientist Dr. Egrie also highlighted the fact that RIA cannot differentiate between biologically active and inactive forms of EPO. (TRX 2069). Dr. Egrie also wrote that you would have to run completely different assays to confirm that immunoreactive material from COS cells was indeed EPO and not some fragment of EPO. (TRX 2063 at p. 348).

It is impossible for persons of skill in the art conducting RIAs, per the claims of the '349 patent, to determine whether and to what extent the RIAs are measuring human EPO, as defined by the Court -- and covered by the claims -- rather than epitopes on fragments. EPO fragments fall outside of the Court's definition of human erythropoietin. The Federal Circuit has held that claims lacked enablement when the patent's specification taught only how to approximate the claimed result. *See Nat'l Recovery Techs., Inc. v. Magnetic Separations Sys., Inc.,* 166 F.3d 1190, 1196-98 (Fed. Cir. 1999) (holding that although the patent specification disclosed a method for detecting signals this method was insufficient to select signals as claimed). Here, an RIA will not give the proper and accurate result of a specific level of EPO (*e.g.* 100 U, as in claim 1) but rather EPO plus other materials that are not human erythropoietin within the scope of the Court's claim construction. This is all the RIA can do since fragments are present, and thus the claim is not enabled.

In addition to the problem with fragments, the claim is also not enabled because the patent does not describe a standard to use in the assay. RIA also requires a standard against which to compare results. (*See* Flavell 1290:13-18). Yet the Lin patent specifies no standard. By Amgen's own admission, there were discrepant measurements of units of EPO from lab to lab, due in part to lack of correlation between standards. (TRX 2065). In her EPO assays, Dr. Egrie used Dr. Goldwasser's pure human urinary EPO standard, "CAT-1", which was no longer available after September 1984. (Egrie 1187:7-10; TRX 2064). Amgen even had a difficult time using the International Standard, and instead began calculating its own units. (TRX 2065). Moreover, the evidence is clear that Amgen understood the importance of specifying a particular standard, as it did

in its FDA submissions and various publications. (TRX 2057:59-60; TRX 2096; TRX 2058.2). The enablement test requires that one of skill in the art need not engage in undue experimentation. Without knowledge of which standard to use for the RIA, *no amount* of experimentation would enable one of skill to know if the amount of EPO required by the claims was actually measured.

Importantly, absolutely none of this evidence was contradicted by Amgen. Indeed, Amgen presented no evidence whatsoever, let alone credible evidence, to defeat Roche's clear and convincing evidence. Accordingly, a reasonable jury could only conclude conclude, based on the evidence, that the patent specification is not enabling.

D. A Reasonable Jury Would Conclude That Claim 7 Of The '349 Patent Is Invalid For Lack Of Written Description Or Enablement Based on "Vertebrate Cells"

Based on the evidence of record, a reasonable jury would conclude that claim 7 of the '349 patent is invalid for lack of written description or enablement for the term "vertebrate cells." Amgen improperly suggests that Roche cannot meet its burden on this issue because Drs. Kadesch and Nunberg did not testify during Roche's case-in-chief. (D.N. 1137-2 at 35). As Roche explained in its prior submissions, however, a jury can decide issues of invalidity based on the documents in evidence, with no need for expert testimony. *See Harvestall Indus., Inc. v. Hochstetler*, 656 F.2d 1232, 1236 (7th Cir. 1981); (*see also* D.N. 1141-6).

Claim 7 requires the culturing of "vertebrate cells." (TRX 4). Vertebrate cells encompass a broad class of different cell-types, including mammalian cells, non-mammalian cells, COS cells and CHO cells. (*See* Lowe 291:4-7, 320:20-24). Yet, it is clear from the face of the patent that the *only* vertebrate cells exemplified are COS and CHO cells. (*See* TRX 4 at col. 10:40, Examples 6, 7, 8, 10). Even assuming, *arguendo*, that use of COS and CHO cells is adequately described and enabled by the specification within the meaning of Section 112 (which it is not), a person of ordinary skill in the art would not interpret such description as universally applicable to all vertebrate cells. Indeed, Amgen's own expert, Dr. Varki, testified that there are over 30,000 different mammalian cells -- a

subset of vertebrate cells -- which have different properties, some of which would be useful for expressing proteins and some of which would not. (Varki 2247:16-2249:16). Moreover, Dr. Lin testified that when he was looking for cells for protein expression, he was concerned about the stability of different cell lines, and his friend at the ATCC told him about two stable cell lines in the class of mammalian cells (a subset of vertebrate cells), including CHO cells. (Lin 1854:13-1857:5). Accordingly, as Dr. Lin admits, not all vertebrate cells (or even all mammalian cells) would work for the intended purpose. Dr. Harlow provided similar testimony, noting the "different cells in different cell lines affect post-translational modifications differently." (Harlow 1794:20-22). The variability in the properties of vertebrate cells is further evidenced by the fact that in the 1983-84 time period, only a handful of vertebrate and mammalian host cells, including CHO cells, were used to express biologically active glycoproteins. (*See* TRX 2026, 2027; Lowe 175:19-176:1). Indeed, there is no evidence in the prior art of using non-mammalian vertebrate cells, such as cells from reptiles or fish, to express glycoproteins, evidencing that a person of ordinary skill in the art would not view these vertebrate cells as useful for expressing biologically active glycoproteins.[32]

Amgen presented no evidence to counter Roche's clear and convincing evidence and, in fact, much of Roche's evidence on this issue came directly from Amgen's own admissions. Accordingly, a reasonable jury would only conclude that description of COS and CHO cells does not constitute description or enablement of the much broader class of vertebrate cells.

VII. CONCLUSION

Based on the foregoing, the Court should grant judgment as a matter of law on all of invalidity defenses and deny Amgen's motion for judgment as a matter of law.

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[32] Indeed, if all vertebrate cells had the same properties such that they would be useful in expressing biologically active glycoproteins, no doubt Dr. Lin would have chosen a cell other than CHO cells, one of the few host cells well-described in the prior art.

CERTIFICATE PURSUANT TO LOCAL RULE 7.1

I certify that counsel for the parties have conferred in an attempt to resolve or narrow the issues presented by this motion and that no agreement could be reached.

Dated: October 4, 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)
Robert L. Kann (BBO# 258025)
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

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/s/ Nicole A. Rizzo
Nicole A. Rizzo

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