UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN INC.'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW PURSUANT TO RULE 50(a)

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I. LEGAL STANDARDS

Federal Rule of Civil Procedure 50(a)(1) provides:

> If a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for the party on that issue, the court may: (A) resolve the issue against the party; and (B) grant a motion for judgment as a matter of law against the party on a claim or defense that, under the controlling law, can be maintained or defeated only with a favorable finding on that issue.

"[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). The standard for granting judgment as a matter of law is high.[1] To affirm the withdrawal of any claim from the jury, the Court must find that the record would permit a reasonable jury to reach only one conclusion on that issue.[2] In ruling on the motion, the Court must consider the evidence and reasonable inferences in the light most favorable to the non-moving party.[3]

However, in order to warrant submission of an issue to the jury, Roche must present "more than a mere scintilla" of evidence and may not rely upon conjecture or speculation.[4] In addition, in a case such as this where Roche bears the heightened burden of proving invalidity by clear and convincing evidence, the Court should take into account the underlying burden of proof in ruling on the motion for judgment.[5] ("[W]e conclude that the determination of whether a given factual dispute requires submission to a jury must be guided by the substantive evidentiary standards that apply to the case. This is true at both the directed verdict and summary judgment stages."). Thus, the relevant inquiry is whether a jury applying the clear and convincing

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[1] The standard for granting judgment is higher if the movant is the party which bears the burden of proof. *Fireman's Fund Insurance Co. v. Videfreeze Corp*., 540 F.2d 1171, 1177 (3d Cir. 1976). Here, of course, Roche bears the burden of proving invalidity by clear and convincing evidence.

[2] *Richmond Steel, Inc. v. Puerto Rican Am. Ins., Co*., 954 F.2d 19, 22 (1st Cir. 1992).

[3] *Keisling v. SER-Jobs for Progress, Inc.*, 19 F.3d 755, 760 (1st Cir. 1994).

[4] *Richmond Steel*, 954 F.2d at 22.

[5] *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

evidence standard could reasonably find for Roche. *Id*. at 255-56.

II. ROCHE HAS FAILED TO PRESENT EVIDENCE FROM WHICH A REASONABLE JURY, APPLYING THE STATUTORY PRESUMPTION OF 35 U.S.C. § 282, COULD CONCLUDE THAT ANY OR ALL OF AMGEN'S CLAIMS IN SUIT ARE OBVIOUS

Roche's arguments that Dr. Lin's patent claims were obvious in view of the prior art were presented by Dr. Lowe and Dr. Bertozzi.

Dr. Lowe gave his opinion that cloning the EPO gene would have been obvious in 1983 and that the use of that gene to produce a biologically active EPO product would have been obvious in 1984.[6] Significantly, Dr. Lowe admitted on cross-examination that his opinions rested entirely on his assumption that cloning the EPO gene was obvious in 1983, and that he had no opinion about the obviousness of Lin's glycoprotein and process inventions if the EPO gene was not available to skilled workers in 1983/84 as state of the art.[7] In reaching his opinions, Dr. Lowe relied only on the Miyake paper and the general cloning art. Not only are such "obvious to clone" opinions legally insufficient to meet Roche's burden, but all of the references that Lowe relied upon were submitted to and considered by the PTO.[8] In such circumstances, Roche's burden under 35 U.S.C. § 282 to prove the obviousness of Lin's invention is "especially difficult,"[9] and the proof Roche has presented at trial is insufficient as a matter of law to establish the obviousness of Lin's EPO DNA.[10]

It is important to recognize that Lin's process and product claims require the possession of EPO DNA as one of several limitations that must be met to establish the defense of

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[6] 9/6/07 Trial Tr. at 257:10-258:12; 259:1-8; 9/7/07 Tr. at 369:7-370:12.

[7] 9/7/07 Trial Tr. 369:7-370:12.

[8] 9/7/07 Trial Tr. 386:1-10.

[9] *Hewlett Packard Co. v. Bausch & Lomb Inc*., 909 F.2d 1464, 1467 (Fed. Cir. 1990); American *Hoist & Derrick Co. v. Sowa & Sons, Inc*., 725 F.2d 1350, 1359 (Fed. Cir. 1984).

[10] *Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991); *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1985); *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).

obviousness. For example, claim 3 of the '933 Patent requires: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." For this reason, it is incumbent on Roche to establish that the invention as a whole, including possession of the EPO DNA, would have been obvious to those of skill in the art in 1983-1984. Roche's failure to carry that burden is fatal to its obviousness defense.

As a second prong of its obviousness case, Dr. Bertozzi testified that Goldwasser's urinary EPO rendered the asserted Lin claims obvious. Notably, Dr. Bertozzi acknowledged that Goldwasser's urinary EPO was a mixture of different EPO glycoforms,[11] that Goldwasser's mixture of EPO glycoforms differed from the mixture of EPO glycoforms in the commercial embodiment of Lin's claims,[12] that the average specific activity of Goldwasser's urinary EPO was less than half that of Amgen's recombinant EPO,[13] and that she had not performed any empirical comparison of Goldwasser's urinary EPO to any other embodiment of Lin's claimed inventions.[14] Nor did Dr. Bertozzi identify the distribution of glycoforms present in Goldwasser's urinary EPO, how one skilled in the art as of 1983/84 would have modified Goldwasser's preparation to duplicate any recombinant EPO preparation, or how or why one skilled in the art as of 1983/84 would have made any recombinant EPO that duplicated Goldwasser's urinary EPO preparation. Dr. Bertozzi's opinions that it would have been obvious in 1983/84 to make a recombinant EPO in some unspecified way that would be identical to Goldwasser's urinary EPO failed to provide any specifics on how she would modify any host cell in order to produce a recombinant EPO like urinary EPO. Moreover, just as Lowe's

[11] 9/24/07 Tr. 1138:1821.

[12] 9/14/07 Tr. 1114:11-1115:6; 1116:7-19.

[13] 9/14/07 Tr. 1095:19-1096:20; 1115:7-1116:6.

[14] 9/14/07 Tr. 1074:8-15.

opinions depend on his assumption that Lin's EPO DNA was obvious and therefore available as prior art, so too do Bertozzi's. She offered no means to produce a recombinant EPO product that would duplicate Goldwasser's product other than the use of Lin's cloned EPO DNA. Like Dr. Lowe's opinions, such unsubstantiated and cursory opinions are legally insufficient to meet Roche's burden on obviousness.

A. ROCHE FAILS TO SHOW THAT CLONING OF THE EPO GENE WAS OBVIOUS

Dr. Lowe testified that if one of skill in the art had the EPO protein, there were methods available in the art in 1983-84 to sequence the protein and then clone the EPO gene.[15] And, according to Dr. Lowe, once one had the gene, then expression of a biologically active protein was also obvious: "My opinion is that if you had the protein, you get the sequence, clone the gene, put it into the cells and the cells will be expected to make biologically active EPO.[16] Dr. Lowe admitted that he had no opinion and offered no testimony on the obviousness of producing a recombinant EPO glycoprotein without possession of the human EPO gene.[17] Thus, if Roche fails to meet its burden of proving by clear and convincing evidence that cloning the human EPO gene was obvious at the time of Dr. Lin's inventions, then Roche has failed to demonstrate that any of Amgen's asserted claims are invalid for obviousness.[18]

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[15] Dr. Lowe testified that "[m]y opinion is that it is obvious if you have the protein sequence of this protein in 1983 to be able to clone the EPO gene." 9/7/07 Trial Tr. 369:7-12.

[16] 9/7/07 Trial Tr. 370:3-5.

[17] This point was brought home when he was asked what if one did not have the gene?

> "Q. Would it then be obvious to make a recombinant EPO glycoprotein that would work in the body to stimulate the production of red blood cells?

A. Honestly, I haven't considered that, that possibility. It hasn't been part of my expert sort of examination." 9/7/07 Trial Tr. 370:6-12.

[18] As discussed, Roche cannot argue that the asserted claims of the patents-in-suit do not implicate the EPO gene. '933 independent claim 3 claims "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin. . . ." '868 Claim 1 also references "growing mammalian host cells transformed or transfected with an isolated DNA sequence

First, it is important to recognize that the obviousness arguments advanced here, together with the references cited by Dr. Lowe, were considered and rejected by the PTO, making the hill Roche must climb to establish this defense especially steep. Second, Dr. Lowe's opinion is flawed ***as a matter of law,*** because a prima facie showing of obviousness requires that the DNA sequence itself be in the prior art, ***not*** merely methods for obtaining it. Third, Roche is collaterally estopped from challenging the obviousness of the cloning of the EPO gene because of the outcome of the prior C*hugai* litigation and the resolution of the three interferences.

1. The References Cited by Dr. Lowe Were All Previously Considered by The U.S. Patent and Trademark Office in Examining Dr. Lin's Patents

Roche's burden of proving obviousness is a high one – particularly so where each of the prior art references it now relies on has been considered by the Examiner and overcome in the prosecution of the patents-in-suit. The Federal Circuit has recognized that the "presumption of validity under 35 U.S.C. § 282 carries with it a presumption that the Examiner did his duty and knew what claims he was allowing."[19] Moreover, a challenger's burden is "especially difficult when the prior art was before the PTO examiner during prosecution of the application."[20]

Roche's expert, Dr. Lowe, admitted on cross-examination that each of the references he relied upon for his obviousness testimony was placed before the Examiner during prosecution of

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encoding human erythropoietin . . . ." '698 Claim 6 references "growing vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of Figure 6 . . . ." '349 Claim 7 which depends on claim 1 references "cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin."

[19] *Intervet Am., Inc. v. Kee-Vet Labs., Inc*., 887 F.2d 1050, 1054 (Fed. Cir. 1989).

[20] *Hewlett-Packard Co. v. Bausch & Lomb Inc*., 909 F.2d 1464, 1467 (Fed. Cir. 1990). *See also American Hoist & Derrick Co. v. Sowa & Sons, Inc*., 725 F.2d 1350, 1359 (Fed. Cir. 1984) ("When no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.").

Dr. Lin's patents in suit.[21] Trial Exhibit 2009 shows that Examiner Martinell, Ph.D., acknowledged that he had reviewed and considered the prior art references cited therein.

Dr. Lowe offers no new evidence of obviousness. He has no personal knowledge relevant to the topic of the production of any *in vivo* biologically active recombinant glycoprotein – let alone EPO – at the time of Dr. Lin's inventions. Dr. Lowe admitted that at the time of Dr. Lin's inventions he had never produced a recombinant glycoprotein in a mammalian cell.[22] In fact, Dr. Lowe admitted that at the time of Dr. Lin's inventions he had never produced any kind of recombinant protein in a mammalian cell.[23] Moreover, Dr. Lowe has never studied or worked with EPO.[24] His only knowledge buttressing his obviousness opinion of producing a functional recombinant human EPO is synthetic – selected and provided to him by Roche's counsel in preparation for his testimony in this case.

Without some new or additional evidence of the scope and content of the prior art as compared to Dr. Lin's claimed inventions, there is simply insufficient evidence for a reasonable jury to conclude that Roche has met its burden of overcoming the presumption of validity and proving by clear and convincing evidence that Dr. Lin's claims-in-suit are obvious.

2. A Prima Facie Showing of Obviousness For a DNA Sequence Requires That There be a Similar Structure in the Art, Not Merely a Method for Obtaining the Structure

In asserting the claims in suit to be obvious, Roche has failed to provide sufficient evidence that cloning the EPO DNA would have been obvious in 1983.[25] Roche's proof that there allegedly were methods for discovering the EPO DNA sequence is legally insufficient

[21] 9/7/07 Trial Tr. 379:9-380:21.

[22] 9/7/07 Trial Tr. 397:4-6.

[23] 9/7/07 Trial Tr. 396:23-397:3.

[24] 9/7/07 Trial Tr. 435:19-436:19.

[25] 9/5/07 Trial Tr. 176:6-14; 178:19-22; 179:17-180:3; 181:4-10; 184:11-16; 188:19-189:15; 206:7-207:11; 207:22-208:22; 210:5-21; 9/6/07 Trial Tr. 217:23-218:11; 219:10-15; 225:17-24;

because a prima facie showing of obviousness requires that the DNA sequence itself be in the art, not merely methods for obtaining it.

Dr. Lowe admitted during his testimony that such structures were absent:

- Dr. Lin was the first to obtain an isolated DNA encoding EPO and thus the DNA's structure was not in the art.[26]
- The complete amino acid sequence for EPO was unavailable and unknown in 1983-84.[27]
- The small amount of amino acid sequence that was publicly available for the EPO protein was incorrect.[28]

The Federal Circuit's decisions in *Amgen v. Chugai* ("*Amgen*"), *In re Bell*, and *In re Deuel* all stand for the principle that evidence of processes for discovering a DNA sequence is legally insufficient to establish obviousness of a DNA molecule.[29] This requirement is consistent with the *en banc* decision in *In re Dillon* that a *prima facie* showing of obviousness for chemical compounds requires showing a "structural similarity" between the claimed compounds and a prior art compound.[30] Just three months ago the Federal Circuit's *Takeda* decision reaffirmed this structural requirement in light of the Supreme Court's *KSR* decision.[31]

Both before this Court and in the Federal Circuit, the nonobviousness of Dr. Lin's EPO DNA was litigated extensively in the earlier *Amgen v. Chugai* litigations. Roche raises the same general arguments that were raised there, namely, whether it was obvious to clone the EPO DNA sequence using cloning or sequencing techniques known in the art. This Court found that it was

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236:10-22; 238:10-240:5; 255:2-18; 256:14-19; 9/7/07 Trial Tr. 369:6-19.

[26] 9/7/07 Trial Tr. 461:21-462:9.

[27] 9/7/07 Trial Tr. 472:15-22.

[28] 9/7/07 Trial Tr. 474:4-11.

[29] *Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991); *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1985); *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).

[30] *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*).

[31] *Takeda*, 492 F.3d at 1356, (*citing In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)); *see also Yamanouchi Pharm. Co. v. Danbury Pharmacal*, 231 F.3d 1339 (Fed. Cir. 2000); *In re*

not.[32] The Federal Circuit's 1991 *Amgen* decision affirmed this Court after reviewing the cloning art and the specific evidence provided. In doing so, the *Amgen* court reserved the issue of whether the EPO gene product itself was obvious aside from the alleged obviousness of a method of making it:

> We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.[33]

The portion of the *Amgen* decision addressing conception confirms that processes for making a chemical compound are insufficient to teach the compound. The *Amgen* court held that conception of the EPO DNA sequence structure requires a complete "mental picture" of the gene's chemical structure that cannot occur until the gene structure itself is isolated:

> Conception does not occur ***unless one has a mental picture of the structure of the chemical***, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. ***We hold that when an inventor is unable to envision the detailed constitution of the gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.***[34]

Mayne, 104 F.3d 1339 (Fed. Cir. 1997).

[32] *Amgen Inc. v. Chugai Pharm. Co. Ltd.*, 1989 U.S. Dist. LEXIS 16110 (D. Mass. Dec. 11, 1989).

[33] *Amgen Inc. v. Chugai Pharm. Co., Ltd*, 927 F.2d 1200, 1207 n.3 (Fed. Cir. 1991).

[34] *Amgen*, 927 F.2d at 1206 (emphasis added). This holding of *Amgen*, that the complex EPO gene could not be conceived until its chemical sequence had been reduced to practice, is binding on the parties on principles of *stare decisis*. *Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557, 1570-71 (Fed. Cir. 1993); *Amgen Inc. v. F. Hoffman-La Roche Ltd*., 494 F.Supp.2d 54, 60-61 (D. Mass. 2007).

"What cannot be contemplated or conceived cannot be obvious."[35] Conception is a matter of law.[36]

Two years later, the Federal Circuit took up the question directly of whether a *prima facie* showing of obviousness of an unknown DNA sequence could be made when only general DNA cloning art was invoked. In *In re Bell*, the Federal Circuit rejected the argument that methods for discovering a DNA sequence are relevant to a *prima facie* showing of obviousness to the specific gene:

> Finally, the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by Weissman. The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made. *See In re Thorpe*, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production.").[37]

Similarly, in *Deuel*,[38] the Federal Circuit rejected the argument that the cDNA structures encoding for a protein were *prima facie* obvious based on a method for discovering the DNA molecules: "Deuel argues that the PTO has not cited a reference teaching cDNA molecules, but instead has improperly rejected the claims based on the alleged obviousness of a method of making the molecules. We agree."[39] The *Deuel* court explained that "[b]ecause Deuel claims

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[35] *Deuel*, 51 F.3d at 1558. *See also Fiers v. Revel* "We thus determined [in Amgen] that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility."

[36] *See Singh v. Brake*, 222 F.3d 1362, 1367 (Fed. Cir. 2000).

[37] 991 F.2d 781, 785 (Fed. Cir. 1993). If only a partial amino acid sequence is in the art, that too is insufficient to place one in possession of the genus of a DNA sequence encoding for the full protein. *In re Wallach*, 378 F.3d 1330, 1333 (Fed. Cir. 2004); *Deuel*, 51 F.3d at 1559. *See also, Rengents of the Univ. of Cal. v. Monsanto*, Co. 2005 U.S. Dist. LEXIS 40379, *35 (N.D. Cal. 2005) (applying *Deuel* and *Bell* to find non-obviousness of claimed DNA molecules).

[38] It bears emphasizing that the Federal Circuit cases arising from the Board of Patent Appeals and Interferences were reviewing a *prima facie* showing of obviousness based on the preponderance of evidence standard. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992). The standard here, of course, is clear and convincing evidence.

[39] *Deuel*, 51 F.3d at 1557.

new chemical entities in structural terms, a prima facie case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art."[40] Looking to the art, the *Deuel* court found no evidence of structurally similar cDNAs even though partial amino acid sequence information was available in the art:

> Here, the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious. Maniatis suggests an allegedly obvious process for trying to isolate cDNA molecules, but that, as we will indicate below, does not fill the gap regarding the subject matter of claims 5 and 7.[41]

The *Deuel* Court concluded that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would be obvious . . . ."[42] That is all the evidence that Dr. Lowe submitted here – general methods of cloning other DNAs. Dr. Lowe provided no structural basis for his opinion that the cloning of the EPO gene was obvious. Again, as Dr. Lowe recognized, he had no opinion if the EPO gene was not available.

At oral argument on September 24, 2007, Roche made two contentions that do not overcome the requirement that DNA structures be in the prior art. First, Roche asserted that the background of the patents-in-suit state that "if you had the entire protein sequence you can make the synthetic DNA obviously."[43] This contention is irrelevant because prior to Dr. Lin's inventions, the entire EPO protein sequence was unknown. Further, the background states that "the direct manufacture of DNA sequences is not possible" without knowing the entire protein

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[40] *Id.*

[41] *Id.* at 1558.

[42] *Id.* at 1559. In view of the Supreme Court's *KSR* decision, three months ago, the Federal Circuit reaffirmed *Deuel's* and *Dillon's* focus on "an established structural relationship between a prior art compound and the claimed compound." *Takeda*, 492 F.3d at 1356. Thus, *KSR* does not impact the applicability of these chemical composition cases.

[43] Trial Tr. at 1321:2-6.

sequence, which is the uncontroverted case here.[44]

Second, Roche incorrectly asserted that Dr. Fritsch's work is Section 102(g) prior art because he allegedly conceived and reduced to practice the inventions covered by the patents-in-suit before Dr. Lin's November 30, 1984 filing date.[45] The Federal Circuit, this Court, and three separate panels of the Board of Patent Appeals and Interferences all found that Dr. Lin conceived and reduced to practice each of the inventions covered by the patents-in-suit before Dr. Fritsch isolated the EPO gene in August 1984. As set forth in the Court's *Amgen v. Chugai* decision: 1) the successful cloning of the EPO gene took place in early October 1983; 2) on February 13 and 14, 1984, Amgen conducted experiments to show the recombinant human EPO produced in COS cells was biologically active; and 3) by May 2, 1984, human rEPO had been expressed in CHO cells.[46] Amgen renews its request for judicial notice of these adjudicative facts.[47] Roche's assertion that Dr. Lin's invention date is the November 30, 1984 filing date of his last application is specious and it cannot place the EPO DNA sequence in the prior art.

During cross-examination, Dr. Lowe admitted that before Dr. Lin's invention, the first 26 amino acids of human EPO were published to the world.[48] Yet even with the published protein sequence information (obtained from Dr. Goldwasser's urinary EPO), Dr. Lowe testified that the codon degeneracy of the known amino acid sequence would not allow a skilled artisan to design

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[44] *See e.g.*, U.S. Patent No. 5,547,933 at col. 3:38-43. Tellingly, Dr. Lowe's obviousness opinion was based on obtaining sufficient amino acid sequence to design probes to screen a cDNA library and clone the gene rather than to synthesize it as Ms. Ben-Ami represented. *Compare* Trial Tr. at 1321:10-21with Trial Tr. at 257:12-21.

[45] Trial Tr. at 1322:18 – 1323:4.

[46] 1989 U.S. Dist. LEXIS 16110 (D. Mass. 1989).

[47] *See* (D.I. 1031 at 2-3, fn. 10-11.) This pending bench memorandum further addresses why Dr. Fritsch's efforts cannot constitute 102(g) prior art because Dr. Lin conceived and reduced to practice each of the inventions several months before Dr. Fritsch admitted that he had first cloned the EPO DNA.

[48] 9/7/07 Trial Tr. 426:8-427:9 (referencing TX 12 at 3651).

a perfectly matching oligonucleotide probe.[49] Given the known degeneracy between the amino acid sequence and the DNA sequence for EPO, with few exceptions, there are multiple codons that code for each amino acid. As a result, Dr. Lowe admitted that most people of skill in the art would stop trying to design probes to clone the EPO gene once they got to about the second amino acid residue due to this degeneracy.[50]

3. Roche is Collaterally Estopped From Arguing that Cloning the EPO Gene was Obvious

Roche is collaterally estoppel from challenging the previously adjudicated non-obviousness of the DNA sequence encoding human erythropoietin and the non-obviousness of the claimed recombinant human EPO.[51] These issues were decided against Roche's Chugai subsidiary before this Court in *Amgen v. Chugai*, and named defendant Roche Diagnostics GmbH (then Boehringer Mannheim) fully participated with its Joint Venture partner Genetics Institute ("GI") in prior litigations that were finally settled in 1993. As set forth in full detail in the papers in support of Amgen's Motion in Limine No. 17, the doctrine of collateral estoppel prevents Roche from taking a second bite at the apple by relitigating these issues here.[52] Amgen incorporates by reference those briefings and refers the Court generally to them.

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[49] 9/7/07 Trial Tr. 428:6-19.

[50] Trial Tr. 435:5-18.

[51] In the prior *Amgen v. Chugai/GI* case, this Court and the Federal Court held that Dr. Lin's EPO DNA invention was nonobvious over the prior art methods of discovering human genes. Also, in the prior *Fritsch v. Lin* interference, the PTO determined that Dr. Lin's recombinant human EPO was structurally different from urinary EPO, and these differences made recombinant EPO novel and nonobvious over uEPO.

[52] By order dated September 24, 2007, the Court denied Amgen's Motion *in Limine* No. 17 to Exclude Roche from Presenting Evidence to Challenge the Non-Obviousness of the DNA Sequence Encoding for Human Erythropoietin in 1983. Apart from the Court's ruling on the evidentiary issue, Amgen believes that, for the reasons discussed herein, judgment as a matter of law on the collateral estoppel issues is appropriate. *See* Amgen's Motion *in Limine* No. 17 and Reply Memorandum in Support of Motion *in Limine* No. 1 for a more complete discussion on collateral estoppel. (D.I. 876-78; 1003, attachment 1.)

Collateral estoppel applies because Chugai and GI were "virtual representatives" of Roche.[53] Roche now owns Chugai and Boehringer Mannheim (now named defendant Roche Diagnostics, GmbH).[54] Virtual representation is an *equitable theory*.[55] First Circuit case law is clear that Roche cannot game the system and exploit its technical "nonparty" status to evade the equitable reach of the collateral estoppel doctrine. Indeed in *Gonzalez*, the First Circuit noted that the balance of equities is tipped in favor of preclusion where, as here, a party engages in "tactical maneuvering designed unfairly to exploit technical nonparty status in order to obtain multiple bites of the litigatory apple."[56]

The balancing of the equities favors preclusion. Roche's attempt to distance itself from its subsidiaries and avoid collateral estoppel is pure gamesmanship and contrary to the law of this Circuit. At the time Roche acquired Chugai and Boerhinger Mannleim, Roche was on ***full notice*** of Chugai and GI's prior litigation with Amgen, and the relationship of Boerhinger Mannheim with GI. Thus, Roche consummated these transactions knowing that Chugai and GI lost the very claims Roche now seeks to relitigate, and now that loss also affected Boerhinger Mannheim. There is no basis in law or equity for indulging Roche's attempt to have its "relitigation" cake and eat it too.[57]

This case cries out for the application of collateral estoppel. Roche acquired the two

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[53] *See Gonzalez v. Banco Cent. Corp*., 27 F.3d 751, 758 n.5 (1st Cir. 1994); *Tyus v. Schoemehl*, 93 F.3d 449, 453-54 (8th Cir. 1996).

[54] Roche is licensed under various GI Patents to sell erythropoietin as a successor in-interest to an October 8, 1985 License Agreement between GI and Bochringer Mannheim. (See 6/01/01 Settlement Agreement between Roche, Kirin-Amgen, and Johnson & Johnson, at p. 1, Amgen Tr. Exh. AYQ (AM44 0230110-121); *see also* 10/08/85 Development and License Agreement between Boehringer Mannheim GMBH and Genetics Institute, Inc. (D.I. 878, Exh. 8); 05/26/97 Press Release entitled "Roche acquires Boehringer Mannehim Group (D.I. 87, Exh. 24)).

[55] *See Gonzalez*, 27 F.3d at 761.

[56] *Id.*

[57] Indeed, during this very litigation Roche has attempted to reap the rewards of its subsidiaries' prior litigation by moving to invoke issue preclusion against Amgen on the basis of the *Chugai* and *GI* litigation. *See, e.g.*, Roche's Motion in Limine (D.I. 801).

entities that litigated against Amgen directly or through GI on the very issue it seeks to relitigate – whether the EPO DNA sequence was obvious based on the prior art of general cloning technology. Effectively no new arguments have been presented, and further judicial resources should not be spent on this issue. Collateral estoppel bars Roche's obviousness claims based on cloning the DNA sequence.[58]

B. DR. LOWE'S TESTIMONY PROVIDES INSUFFICIENT BASIS FOR A REASONABLE EXPECTATION OF SUCCESS IN EXPRESSING THE EPO GENE IN MAMMALIAN CELLS AND PRODUCING ISOLATABLE QUANTITIES OF A GLYCOSYLATED EPO PRODUCT HAVING IN VIVO BIOLOGICAL ACTIVITY

While the cloning of the EPO gene is a critical piece of Roche's obviousness arguments, the asserted claims of the patents-in-suit are not to the DNA but to (1) processes for making isolatable quantities of glycosylated EPO having *in vivo* biological activity (the '868, and '698 patents), or a process for making EPO using vertebrate cells having the capacity to produce relatively large amounts of EPO (the '349 patent); and (2) EPO product claims defined again by the *in vivo* biological activity and characterized by being the product of certain process and source limitations (the '422 and '933 patents). To meet its burden of showing obviousness of the asserted claims, in addition to showing that the cloning the EPO gene was obvious, Roche must also show that there was a reasonable expectation of producing isolatable quantities of biologically active EPO products. While Dr. Lowe said those words, the evidence he relied upon was woefully inadequate to support such a conclusion especially given that the PTO considered the same references that Dr. Lowe relied upon.

Dr. Lowe cited to Genentech's work on the production of recombinant tPA, but as Lowe admitted on cross-examination, there was no evidence in the prior art tPA patent application showing that the recombinant tPA had activity.[59] In fact, that tPA patent application confirmed

[58] To the extent the Court requires an evidentiary hearing, or this issue that is a matter of law, it should be scheduled at a late date so that any necessary witness may be subpoenaed.

[59] 9/7/07 Trial Tr. 389:13-19.

that the state of the art was entirely unpredictable:

> "However, on an individual product basis, the pathway remains somewhat tortuous and the science has not advanced to a stage where regular predictions of success can be made. Indeed, those who portend successful results without the underlying experimental basis do so with considerable risk of inoperability."[60]

The other references cited by Lowe were the Farber abstracts cited at Column 9, lines 42-63 of the '933 patent. In these references, human kidney mRNA was inserted into frog oocytes and some small amount of biological activity was detected in the "translation products." The amount of activity, however, was estimated to be 220 mU (milliunits) which is 500 times less than the lowest production levels recited in the '349 claims (100 U). No product was isolated in the Farber references and Dr. Lowe did not suggest that one could have been. Importantly, Farber does not disclose the production of recombinant EPO, let alone the production of recombinant EPO in quantities sufficient to purify or isolate the EPO from cell culture media.[61] Moreover, Farber's oocyte does not grow continuously so it is particularly ill-suited to produce continuous or high-levels of EPO protein. Given the 500 fold difference in production, the lack of any suggestion that EPO could be isolated and the fact that the reference was before the PTO, it is legally insufficient to support Roche's obviousness arguments.[62]

C. DR. BERTOZZI'S OPINION ON OBVIOUSNESS FAILED TO ADDRESS THE STATE OF THE ART IN 1984 AND A WAY TO ACHIEVE THE CLAIMED INVENTIONS

Dr. Bertozzi stated her opinion that the asserted claims of the '933 and '422 patents were obvious in light of Goldwasser's urinary EPO, but the only evidence she cited to support her conclusion was that recombinant EPO made in mammalian cells had the same glycoform

[60] 9/7/07 Trial Tr. 393:14-20.

[61] TX 2023.

[62] Moreover, the Farber abstract would have been disregarded by the ordinarily skilled person, as abstracts are not peer reviewed and lack substantiation in the form of detailed methods, results, and interpretation by the authors.

structures as those in Goldwasser's urinary EPO.[63] She testified on direct that: "Goldwasser's EPO has structures that can all be made according to claim 3. So the product of ['933] claim 3 is basically the same as Goldwasser's EPO."[64] While noting the structural similarity between the prior art and the claims, significantly Dr. Bertozzi provided no way to produce the claimed products based on the prior art. Indeed, her testimony was limited to the use of Dr. Lin's invention, '933 claim 3, to make the structures found in urinary EPO. But obviousness must be based on the prior art and not on the claimed invention. It is entirely improper to use the claimed invention as a starting point to make something that is close to the prior art. For this reason alone, Dr. Bertozzi's evidence is legally insufficient to prove obviousness.

The failure of Dr. Bertozzi to cite any prior art methods for making the claimed inventions of the '933 and '422 patents is highlighted even more by the fact that she was not a person of ordinary skill in the art at the time of the inventions in 1983-4. In fact, she was just graduating from high school at that time. The only way she could inform herself of the state of the art is to rely on publications that set forth the state of the art in glycobiology. She failed to cite any such references.

III. ROCHE HAS NOT PRESENTED EVIDENCE FROM WHICH A REASONABLE JURY APPLYING A CLEAR AND CONVINCING STANDARD COULD CONCLUDE THAT THE RECOMBINANT EPO PRODUCTS CLAIMED IN LIN'S '933 PATENT WERE ANTICIPATED BY GOLDWASSER'S URINARY EPO

Roche asserts that claims 3, 7-9 and 12 of the '933 patent and claim 1 of the '422 patent were anticipated by the urinary EPO prepared by Dr. Goldwasser and his colleagues and described in the Miyake 1977 publication. But just as it failed to prove obviousness, Roche's evidence on anticipation was legally insufficient to meet its burden.

Claims 3, 7-9, 11, 12 and 14 of the '933 patent are product-by-process claims, containing

[63] 9/14/07 Trial Tr. 1018: 13-15.

[64] Id. at 14-15.

the limitation "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell…."[65] Similarly, Claim 1 of the '422 Patent requires that the human EPO be "purified from mammalian cells grown in culture." Roche does not dispute that Dr. Goldwasser's urinary EPO preparation does not meet either of those limitations. Roche's Dr. Spinowitz ultimately admitted that Dr. Goldwasser's urinary EPO preparation was not "purified from mammalian cells grown in culture,"[66] and Roche's expert Dr. Bertozzi offered no opinion that Goldwasser's uEPO preparation satisfies the "non-naturally occurring limitation."[67] Also significantly, Dr. Bertozzi gave no opinion as to the anticipation of '422 claim 1 in view of Goldwasser's urinary EPO.[68]

Rather, in asserting its anticipation defense, Roche is left with the argument that the source and process limitations of those claims are irrelevant because, Roche argues, Goldwasser's urinary EPO preparation is identical in structure and function to the embodiments of Dr. Lin's claims. As a result of that alleged identity, Roche says, the source and process limitations do not imbue the claimed inventions with any structural or functional differences from prior art preparations, and thus can be disregarded.

Roche's argument fails because it has not presented clear and convincing evidence from which a reasonable jury could conclude that the prior art preparation is identical to any embodiment within the scope of the claims. On September 24, 2007, Roche counsel argued to the Court that "it is Amgen's burden to show that the source limitation imparts structure,"[69]

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[65] '933 claim 3 expressly contains that limitation. Claims 7-9, 11, 12 and 14 depend on claim 3 and are thus likewise subject to that limitation.

[66] 9/12/07 Trial Tr. 856:19-21, 873:19-24.

[67] 9/14/07 Trial Tr. 1007:23-1008:11.

[68] 9/14/07 Trial Tr. 1024:1-15. The Court sustained an objection that any opinion concerning anticipation of '422 claim 1 was not in Bertozzi's report.

[69] 9/24/07 Trial Tr., 9/24/07, afternoon proceedings, 31:21-22. 9/24/07 Trial Tr., afternoon proceeding, 32:21-22.

citing *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). In fact, the footnote referenced by counsel, footnote 20, states: "We note also that on remand when considering obviousness and anticipation issues relation to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product ***shown to be present in the prior art*** cannot be rendered patentable solely by the addition of source or process limitations."[70] The Court thus made clear that Roche must first prove the claimed product to be in the prior art, a showing for which they bear the burden of proof by clear and convincing evidence.

Beyond that, Roche's argument ignores the evidence that Dr. Lin's human EPO purified from mammalian cells grown in culture differs in important respects from Dr. Goldwasser's urinary EPO product, including differences in glycosylation, conformational structures, and relative potency (specific activity). Indeed, the Board of Patent Appeals and Interferences found that Goldwasser's urinary EPO was not identical to Lin's claimed products,[71] and that Lin's claimed product by process was novel over Goldwasser's urinary EPO product.

Rather than addressing these differences, Roche elicited entirely speculative and conclusory testimony from its expert Dr. Carolyn Bertozzi, to the effect that Goldwasser's urinary EPO and the recombinant EPO products claimed in the '933 patent are "the same" because certain molecules within each are the same, and that she "could" make a population of recombinant rEPO that would be the same in structure and function as the alleged prior art urinary uEPO. This speculative testimony, unsupported by experimentation or other comparative data, is not clear and convincing evidence from which a reasonable jury could find for Roche on anticipation. If credited, it would turn the presumption of validity on its head by leaving it up to Amgen to now offer evidence that one of ordinary skill in 1983-84 "could not" have made a population of recombinant rEPOs that would be identical in structure and function

[70] 314 F.3d at 1354, n. 20 (emphasis supplied).

to Goldwasser's urinary EPO preparation. Amgen's Motion for Judgment as a Matter of Law should be granted.

A. LEGAL STANDARD

The applicable law is clear that source and process limitations may imbue the claimed inventions with structural and/or functional differences that distinguish the claimed inventions over the prior art.[72] This Court has noted that the core issue in the anticipation analysis of '422 claim 1 is whether Lin's claimed invention is novel, that is, whether Dr. Goldwasser's prior art urinary EPO preparation had the identical structure and function as Lin's claimed products.[73] Roche must show that a prior art product either meets the process and source limitations or is identical to something that is made by the recited process or source. As issued United States patents, the claims are entitled to a statutory presumption of validity.[74] Where, as here, the Board of Patent Appeals and Interferences not only addressed whether Goldwasser's urinary EPO anticipated Lin's claimed products, but also considered most if not all of the same evidence now presented by Roche, and based on that evidence decided that Goldwasser's urinary EPO was not identical to Lin's claimed products,[75] the presumption of validity that ordinarily attaches to an issued patent is particularly worthy of respect.[76] Amgen successfully carried its burden

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[71] TX 2011 at AM-ITC 001145-46.

[72] *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 494 F. Supp. 2d 54, 65 (D. Mass. 2007) ("As Amgen correctly states, however, and as has long been recognized by the Federal Circuit, ***source or process limitations*** can and do serve to define the structure of a claimed product where such limitations are the best means to distinguish a claimed product over prior art." (citing *In re Luck*, 476 F.2d 650, 653 (C.P.A. 1973)).

[73] 9/12/07 Trial Tr. 869:4-871:24 ("[T]he factual dispute here is whether it's a new product . . . The jury is going to have to resolve whether the prior art, which I have let in, all right, the so-called prior art, is in fact the same product. If it is, the source limitation won't save them. If it's not, the source limitation is part of the limitation . . .").

[74] 35 U.S.C. § 282; *Sinskey v. Pharmacia Ophthalmics, Inc.*, 982 F.2d 494, 498 (Fed. Cir. 1992).

[75] TX 2011 at AM-ITC 00941239-40.

[76] *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990) citing *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

before the Patent Office, and the burden now falls to Roche[77] to prove by clear and convincing evidence that some particular prior art product was in fact identical in structure and function to something within the scope of the claimed inventions .[78]

B. ROCHE'S DR. BERTOZZI ACKNOWLEDGED DIFFERENCES BETWEEN GOLDWASSER'S UEPO PREPARATION AND THE EMBODIMENTS OF LIN'S CLAIMS

Lin's patent explicitly provided empirical evidence by way of SDS-PAGE to substantiate a structural difference between his claimed products and Dr. Goldwasser's prior art urinary EPO preparation in the extent and proportion of various N-linked carbohydrates attached to the glycoproteins.[79] The details of that difference were later understood in the population differences of the rEPO and uEPO products as confirmed in Amgen's PLA,[80] and relied on by the Board of Patent Appeals and Interferences in deciding that Lin's claimed product was in fact not identical to Dr. Goldwasser's prior art urinary EPO preparation.[81] Furthermore, Dr. Bertozzi admitted that the distribution of glycoforms in Goldwasser's urinary EPO differs from the distribution of glycoforms in CHO cell EPO.[82]

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[77] The *inapposite* authority previously cited by Roche concerns the burden that Amgen successfully carried during the prosecution of its claims to establish their patentability. *In re Marosi*, 710 F.2d 799, 803 (Fed. Cir. 1983); *In re Moeller*, 117 F.2d 565, 935 (C.C.P.A. 1941).

[78] *RCA Corp. v. Applied Digital Data Sys., Inc*., 730 F.2d 1440, 1445 n.3 (Fed. Cir. 1984) ("Because of the statutory presumption, a court is required to assume novelty and then 'must be satisfied . . . that the party challenging validity has carried its burden of overcoming the presumption.'", (quoting *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983))); *Sinskey*, 982 F.2d at 498.

[79] TX 0005 at Col. 28:49-67. The recombinant EPO products were reported as being different from the urinary EPO before and after removal of the sialic acids. Upon removal of the N-linked carbohydrate chains, rEPO and uEPO "resulted in substantially homogeneous products having essentially identical molecular weight characteristics."

[80] TX 2057 at AM-ITC 00092890.

[81] TX 2011 at AM-ITC 001145-46.

[82] 9/14/07 Trial Tr. 1116:10-17 (". . . the mixture of glycoforms that Amgen purified from their CHO cells had different relative amounts of glycoforms compared to the mixture that Goldwasser purified from human urine."); 1127:3-11 ("What the [IEF] test can do is detect an enhancement of certain glycoforms of EPO, and so as I mentioned before, the glycoforms of EPO in the commercial EPO preparations come from CHO cells, and they're purified, so there's

The evidence at trial also reveals a pronounced and critical functional difference – that is, the significant difference in potency between Goldwasser's urinary EPO and Lin's claimed products,[83] a difference that Roche's Dr. Bertozzi admitted and attributed to a "misfolding" of Goldwasser's urinary EPO product.[84] But whatever structural or conformational difference accounts for the critical difference in potency, Roche certainly has produced no evidence that it is not attributable to the difference in source from which Goldwasser's prior art product was obtained.

C. ROCHE HAS FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE THAT GOLDWASSER'S URINARY EPO PREPARATION IS IDENTICAL TO ANY EMBODIMENT OF LIN'S CLAIMS

As discussed, Roche must prove by clear and convincing evidence that Goldwasser's urinary EPO preparation, as the alleged prior art, is identical in structure and function to a recombinant EPO product with the scope of Lin's claims. If it cannot, then the source and process limitations in the '933 and '422 Patents, discussed above, are fatal to Roche's anticipation defense, since it is undisputed that the alleged prior art EPO does not satisfy those limitations.

In its effort to demonstrate that identity, Roche relies principally on its expert, Dr. Bertozzi, who (1) admits that Amgen's recombinant EPO is different than Goldwasser's uEPO, as shown above, (2) cites to no actual recombinant EPO product that is identical to Goldwasser's uEPO, (3) admits that not all of the glycoform structures in Goldwasser's uEPO have to date been made in mammalian cells, (4) has performed no experiments to support her opinions, and (5) can only offer unsubstantiated speculation and conclusory opinions about what could be

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a limited subset of them in these commercial recombinant EPOs. And the relative proportions of those glycoforms are different enough from the EPO glycoproteins that are collected into the human urine so that one can see an enhancement of those glycoforms when they're mixed together."); 1128:14-22.

[83] TX 2059 at 699; TX 2062 at 247, 249; *see also* 9/14/07 Trial Tr. 1095:9-1097:21.

done. Such evidence is grossly insufficient to establish anticipation.

In her attempts to demonstrate the identity of Goldwasser's uEPO with a product within the scope of Lin's claims, Dr. Bertozzi offered the remarkable admission that only ***some of*** the glycoforms within Dr. Goldwasser's prior art uEPO have actually been made in mammalian cells:

> "And what I'm here to tell you is that that claim describes all recombinant EPOs made in mammalian cells, not just a few of them, but all of them, and all of the glycoforms from Goldwasser's EPO are among that group that can be made in mammalian cells. **And some of them, in fact, have been made in mammalian cells."**[85]

That admission puts in proper context and renders legally inadequate Dr. Bertozzi's testimony that the rest of the glycoforms found in Goldwasser's urinary EPO could hypothetically be made in mammalian cells. In order to prove anticipation of a patent claim, however, a prior art product must be identical to some actual embodiment within the scope of the claim. Not only that, it must exist in one product. Dr. Bertozzi's hypothetical, mix and match approach to glycoforms does not provide an actual, single embodiment to be compared for anticipation purposes. For this reason alone, Roche's evidence is legally insufficient.

Further, Dr. Bertozzi made it clear that, for purposes of her analysis, she considered each separate type of glycoform molecule to be an individual "product":

> Q. All right, Doctor. Let's take that one step at a time, okay? You said that it's the recombinant EPO that has been produced by CHO cells has been characterized?
> A. Yes, it has.
> Q. Okay, Taking that product, putting aside whether there are structures in that product that are the same, ***is the product as a whole identical***?
> ….
> A. It's not really a yes-or-no question. It can't really be answered yes or no because---
> ….

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[84] 9/17/07 Trial Tr. at 1115:7-1116:6.

[85] 9/14/07 Trial Tr. at 1129:4-9.

> Q. Is there anything that differentiates the recombinant human erythropoietin produced by CHO cells, anything, that differentiates it form Goldwasser's prior art urinary EPO?
>
> ….
>
> A. ***Well, the EPO produced by CHO cells is a combination of molecules. So there are many products in there***. There are many glycoprotein molecules, some of them have no distinction from molecules from Goldwasser's EPO. That's what I can say.[86]

Dr. Bertozzi's "many products" opinion, while necessary to her molecule-by-molecule approach, is wholly contrary to the language of the claims. In particular, it distorts the meaning of the phrases "glycoprotein product" and "pharmaceutical composition." Claim 3 of the '933 patent states:

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

'933 claim 9 states:

> A pharmaceutical ***composition*** comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

The claims discussed thus refer either to a "glycoprotein product of the expression" or a "pharmaceutical composition." Dr. Bertozzi herself admitted that erythropoietin is expressed as a mixture of different glycoforms, ***not*** as a single discrete molecule.[87] The claimed "glycoprotein product of the expression" thus necessarily refers to the mixed population of glycoforms expressed. Similarly, the claimed "pharmaceutical composition" necessarily refers

[86] 9/14/07 Trial Tr. 1071:4-1072:21 (emphasis added).

[87] Dr. Bertozzi's testified: "Well, we know that erythropoietin is generally made by mammalian cells as a mixture of glycoforms." 9/14/07 Trial Tr. 1017:21-22. As Dr. Bertozzi explained, glycoforms are "glycoprotein molecules that differ in their structures because their sugars are different. So, glycoforms would be like a set, two glycoforms or two molecules, they're both glycoproteins, and the difference between them is all in the sugar parts." 9/14/07 Trial Tr.

to the totality of erythropoietin molecules that comprise the composition, ***not*** a subset of them.

The correct analysis under the language of the claims requires a comparison of the total population of EPO molecules that comprised Goldwasser's uEPO product with the total population of EPO molecules that comprise a product or composition falling within the scope of Dr. Lin's claims. When Dr. Bertozzi correctly compared ***those*** two populations, she ***admitted*** that the distribution of glycoforms in Dr. Goldwasser's uEPO differs from the glycoform distribution in CHO cell EPO:

> Q. Now, this is a difference, this is a difference that we're looking at here between recombinant human erythropoietin and urinary EPO; correct?
>
> A. What this suggests is that the mixture of glycoforms that Amgen purified from their CHO cells had different relative amounts of glycoforms compared to the mixture that Goldwasser purified from human urine. So in other words, all the data suggests that the structures are the same in the two materials, but that the relative proportions are different. And these data, I would say, concur with that interpretation.
>
> ***So in*** my ***opinion, these are evidence that there is a difference in the proportions, yes***.[88]

In addition, Dr. Bertozzi's testimony makes clear that she was truly speculating about what she might be able to do. Significantly, she admitted that it would be difficult to make a recombinant EPO that was identical to Goldwasser's uEPO using only a single CHO cell – the one used by Lin in his patent, and that she had performed no experiment to substantiate her opinions:

> THE COURT: The question is: You believe that it would be possible, using the teaching of Lin's patent, to make a recombinant EPO that has all of the structures that were present in Goldwasser's urinary EPO; is that correct?
>
> …
>
> A. So, Lin's patent only teaches one particular CHO cell. **And using that single CHO cell, I think it would be difficult to recapitulate Goldwasser's EPO.** I think one would have to use more or different CHO

1017:13-18.

[88] Trial Tr. at 1116:7-19 (emphasis added).

> cells.
> Q. Okay. But it's your opinion that if you tried, you'd be able to do it; is that right?
> A. Yes.
> …
> Q. You have not performed an experiment where you can demonstrate to the jury that you have been able to make a recombinant human EPO that has all of the structures of Goldwasser's urinary EPO, have you?
> …
> A. **I have not done that experiment**.[89]

In addition, Dr. Bertozzi failed to present any evidence demonstrating what populations of molecules or structures were actually present in Dr. Goldwasser's uEPO, or that one of skill in the art in 1983-84 would have known that. Absent such knowledge, even today, it would be an impossible task to produce or select a population of recombinant EPO molecules within the scope of Lin's claims that duplicated the population of molecules that comprised Goldwasser's urinary EPO. And even if one attempted to do so, they would still not be able to duplicate the damaged conformational structure of Goldwasser's uEPO, which Dr. Bertozzi testified likely resulted in its reduced specific activity.[90]

Dr. Bertozzi's opinion does not satisfy the burden of clear and convincing evidence. She identified no recombinant EPO product within the scope of Lin's claims that possessed all of the structures of Goldwasser's urinary EPO preparation, she ran no experiments, she offered no data, and at bottom, offered nothing other than her speculation as to what one "could" do. The presumption of validity cannot be rebutted by such flimsy and speculative evidence, and the Court, respectfully, should find that no reasonable jury, applying a clear and convincing standard, would conclude otherwise.[91]

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[89] 9/14/07 Trial Tr. at 1073:14-1074:15.

[90] 9/14/07 Trial Tr. at 1115:7-1116:6 (emphasis added).

[91] *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, []1186 (Fed. Cir. 2002). There, an expert, testifying on undue experimentation in an enablement context, stated that while he had "'imagined' having seen experiments demonstrating that certain combinations fell within the scope of the salt patents yet failed to yield efficiency enhancing

In addition, and again, the opinion and argument are irrelevant, since under § 102, anticipation is determined as of the date of the invention. Roche provides no evidence, through Dr. Bertozzi or otherwise, that as of 1983-1984, one of skill in the art would have (1) been able to make a recombinant human EPO that had all of the structures of Goldwasser's urinary EPO, or (2) would have been able to duplicate Dr. Goldwasser's urinary EPO population, applying the teachings of Dr. Lin's patents.

Because Dr. Bertozzi's admitted that not all of the structures in Goldwasser's urinary EPO had yet been made by mammalian cells grown in culture and because she relies on an incorrect interpretation of a "glycoprotein product" and "pharmaceutical composition" as a single molecule or a hypothetical uniform population of molecules, Roche has failed to provide clear and convincing evidence that Dr. Goldwasser's urinary EPO product is identical in structure and function to a recombinant EPO product of Lin's inventions . Absent such evidence, Roche's anticipation defense fails.

IV. ROCHE HAS FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE FROM WHICH A REASONABLE JURY COULD FIND THAT THE CLAIMS OF THE '422 OR '933 PATENT ARE ANTICIPATED OR OBVIOUS BASED ON ALLEGED PRIOR ART ADMINISTRATIONS OF EPO

A. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE THAT THE BARON/GOLDWASSER EXPERIMENT SATISFIED THE LIMITATION "THERAPEUTICALLY EFFECTIVE AMOUNT"

If Drs. Baron and Goldwasser had in fact achieved therapeutic efficacy, one would have expected those researchers to publish the results in a scientific journal, not abandon their study.[92]

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catalysts, he '[could not] recall any specifically.'" The court referred to the "general and vague nature of these statements," and found that the district court had not abused its discretion in holding that the jury's verdict of lack of enablement was against the weight of the evidence. *See also Sud-Chemie Inc. v. CSP Techs., Inc.*, No. 4:03-CV-003-SEB-WGH 2006 WL 2246404, at *38 (S.D. Ind. Aug. 4, 2006) ("The sole basis for SCI's contention appears to be the unsupported speculations of Dr. Paul, who did not conduct any experiments himself. These speculations of Dr. Paul and of SCI's attorneys do not constitute sufficient grounds, much less clear and convincing evidence, on which to discount [otherwise credible testimony].").

[92] Amgen will separately move for judgment as a matter of law on the basis that the

Not only was the study abandoned, it was never submitted for peer review or publication.[93] Dr. Baron testified that the results were not clinically significant.[94] Nor is there any evidence of even a single instance in which Dr. Goldwasser's urinary EPO preparation was successfully used to treat any human anemia patient.[95]

Roche argues that an increase in reticulocyte count is evidence that Dr. Goldwasser's urinary EPO compound comprised a therapeutically effective amount of human EPO. If the data from the Baron/Goldwasser experiment clearly showed that reticulocyte count in the three patients went up, then a simple statistical analysis should demonstrate that. But Roche presented no evidence, expert testimony, or testimony from the researchers suggesting that the results of Baron/Goldwasser experiment were statistically significant. In fact, Roche's expert, Dr. Spinowitz, did not perform any statistical analysis of the data,[96] and therefore could not agree that the increase in reticulocytes seen in the patient data was "statistically significant."[97]

Roche offers no testimony to contradict Dr. Baron's testimony that the question mark handwritten on the data reflected that the referenced data point showing a marked increase in reticulocyte count "did not make any sense" in light of the rest of the data.[98] Nor did Roche offer any explanation for why the data showing an increase in reticulocyte count in one patient was contradicted by data from a different lab showing that the reticulocyte count in the very same patient did not increase.[99] As Dr. Spinowitz testified, both labs followed standard

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Baron/Goldwasser experiment is not prior art under 35 U.S.C. §§ 102(a), (b), (f) or (g).

[93] 9/12/07 Trial Tr. 877:4-878:2, 878:9-13.

[94] 9/11/07 Trial Tr. 668:23-669:1.

[95] 9/12/07 Trial Tr. 945:23-946:1.

[96] 9/12/07 Trial Tr. 921:9-16.

[97] 9/11/07 Trial Tr. 918:6-25.

[98] 9/11/07 Trial Tr. 679:10-17.

[99] 9/12/07 Trial Tr. 921:24-924:22.

procedures but came up with two different results,[100] one of which contradicts Roche's argument that reticulocyte count went up.[101]

Roche also cannot avoid the fact that neither Dr. Baron nor Dr. Goldwasser elected to publish the results of their urinary EPO clinical studies.[102] Notably, when asked whether he thought that clinicians would have been interested in the data from the Baron-Goldwasser studies, Dr. Spinowitz admitted that that data was not available prior to 1984 and further admitted that he was unaware who the data was made available to.[103]

In light of Roche's failure to address the contradictory testimony and evidence, Roche's proof that the Baron/Goldwasser experiment elicited an increase in reticulocytes, and was therefore a therapeutically effective amount of human EPO, falls well short of clear and convincing.

V. ROCHE HAS FAILED TO MAKE A SUFFICIENT SHOWING ON A NUMBER OF "LOW HANGING FRUIT" ISSUES

A. ROCHE HAS FAILED TO SHOW THAT GOLDWASSER'S UEPO RESULTED IN AN INCREASE IN HEMATOCRIT IN DIALYSIS PATIENTS

If anything is clear from the results of the Goldwasser/Baron study, it is that there was no increase in the hematocrit of any of the three patients. Dr. Baron reported that: "There was no significant increase in the hematocrit observed."[104]

Nonetheless, Roche persists in arguing that the Goldwasser/Baron study anticipate '933 claims 11 and 14. These claims are both method of treatment claim that recite a method of

[100] 9/12/07 Trial Tr. 926:8-10.

[101] Dr. Spinowitz also failed to take into account or offer an opinion concerning testimony of Drs. Katz and Goldwasser, researchers who conducted the Baron/Goldwasser experiment, that potentially contradicts Roche's arguments concerning the purported increase in reticulocytes. 9/12/07 Trial Tr. 878:20-25; 883:7-885:6.

[102] 09/11/07 Trial Tr. at 669:14-669:20; 877:4-878:13.

[103] 09/11/07 Trial Tr. at 809:3-809:9.

[104] Trial Tr. (9/11/07) 667:19 – 668:12.

treating a kidney dialysis patient "to increase the hematocrit level of said patient." Clearly, this did not happen in the Goldwasser/Baron study.

Instead of relying on the human data that showed no increase in hematocrit, Roche argues the hamster data.[105] But the claim does not recite the treatment of hamsters; the claim is specifically directed to the treatment of dialysis patients. That is who Dr. Baron treated in his study.[106] In the face of negative human data from the precise patients recited in the claims, the hamster data is not legally sufficient to meet Roche's burden of showing anticipation or obviousness of these claims.

B. ROCHE'S ARTIFICIAL CLAIM OF OBVIOUSNESS UNDER SECTION 102(f) THAT THE CLAIMS OF THE PATENTS-IN-SUIT WERE SOMEHOW INVENTED BY OR DERIVED FROM DR. GOLDWASSER FAILS

Roche argues that it would have been obvious for one of ordinary skill, if in possession of sufficient quantities of purified human urinary EPO from Dr. Goldwasser in or before October 1983 to clone the EPO gene and obtain expression in mammalian host cells of the encoded human erythropoietin having in vivo biological activity of the naturally occurring glycoprotein."[107] But Roche goes beyond this position and argues under 35 U.S.C. § 102(f) that Lin "did not invent himself invent the subject matter sought to be patented," but rather, he derived the invention from Dr. Goldwasser. Having this issue in the case allows Roche's counsel to argue, as she did in opening statement, that the patented inventions really should belong to the NIH, the public or the University of Chicago. Since Roche has failed to present any evidence of derivation, it is time to exclude this rhetoric from the case.

The subject matter of the Lin patents is not purified urinary EPO; rather, it is recombinant human EPO and processes for making EPO. There can be no dispute that the only thing Dr.

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[105] See Trial Tr. (9/11/07) 769:22 – 771:25.

[106] Trial Tr. (9/11/07) 769:11 -15; 667:19-23.

[107] D.I. 919 at p. 36 (Roche Pre-Trial Brief).

Goldwasser provided to Dr. Lin was the chopped up pieces of urinary EPO – the first sentence in Example 1 in the patent. There is certainly no evidence, and heretofore no allegation, that Goldwasser actually cloned the gene encoding for human EPO and used it to obtain expression of recombinant EPO in mammalian cells, all of which are subject matters of the patents in suit.

In order to prove that Dr. Lin derived his inventions from another, under 102(f), Roche must prove, by clear and convincing evidence, both a prior conception of each invention by another, and communication of each invention to the patentee.[108] The communication of the invention must be sufficiently clear and complete to enable one of ordinary skill in the art to make the patented invention.[109]

Roche cannot meet its burden. Indeed, the evidence is entirely to the contrary, especially the evidence from Dr. Goldwasser himself. He testified at trial that, other than providing purified human urinary EPO to Amgen, he had nothing to do, and could have had nothing to do, with the Lin inventions. Specifically, he testified that he did not provide any of the protein sequence information to Amgen or to Dr. Lin, that he did not provide anything described in the patents other than the tryptic fragments of urinary EPO (see Example 1 of the specification), that he did not design or make any of the probes that Dr. Lin used to clone the human EPO gene, and that he did not do any of the work to clone the EPO gene.[110] Dr. Goldwasser further testified that he could not have been responsible for the inventions described in the Lin patents:

> "Q. Did you do any of the work to make the genetically engineered cells that could produce recombinant EPO?
> A. No.
> Q. Did you do any of the work to make cells that could produce EPO glycoprotein products that were active in the body?
> A. No.
> Q. Did you make any of the pharmaceutical compositions that are

[108] *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003).

[109] *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1577 (Fed. Cir. 1997).

[110] 9/10/07 Trial Tr. 613:1-24.

described in Dr. Lin's patents containing EPO that works in the body?
A. No.
Q. Did you tell Dr. Lin how to do any of that work?
A. No.
Q. Why not?
A. I didn't know how."[111]

Roche has presented no evidence to the contrary. In particular, it has presented no evidence under section 102(f) that Dr. Lin did not invent or derived from another the subject matter sought to be patented. Consequently, Roche's derivation argument should be dismissed from the case.

C. THE PLASMA EPO STUDIES OF DR. ESCHBACH DO NOT ANTICIPATE CLAIM 1 OF THE '422 PATENT OR CLAIMS 3, 9, 11, 12 AND 14 OF THE '933 PATENT

The plasma EPO studies performed by Dr. Eschbach do not anticipate the claims of the '422 or '933 Patents because Dr. Spinowitz admitted that the sheep plasma and human plasma studies failed to meet several limitations of the asserted claims, and Dr. Spinowitz and Roche failed to establish that the human plasma study is prior art.

1. The Sheep Plasma Study of Dr. Eschbach Does Not Anticipate The Claims of The '422 or '933 Patents

Dr. Spinowitz admitted at trial that the EPO used in the sheep plasma study was not human erythropoietin,[112] was not a pharmaceutical composition,[113] and was not obtained from mammalian cells grown in culture.[114] Claim 1 of the '422 is a pharmaceutical composition of human erythropoietin that is purified from mammalian cells grown in culture.[115] Thus, Dr. Spinowitz admitted at trial that all three of these limitations of claim 1 are not met, and there can

[111] 9/10/07 Trial Tr. 614:4-18.

[112] 9/12/07 Trial Tr. 863:7-17.

[113] 9/12/07 Trial Tr. 946:19-947:2.

[114] 9/12/07 Trial Tr. 863:18-864:1.

[115] The pharmaceutical composition of human EPO is also therapeutically effective and includes a pharmaceutically acceptable diluent, adjuvant, or carrier.

be no anticipation of claim 1 of the '422 Patent by the Eschbach sheep plasma study.

Claims 9, 11, 12 and 14 of the '933 Patent all require a pharmaceutical composition that includes a glycoprotein product of the expression of an exogenous DNA encoding human erythropoietin. Dr. Spinowitz admitted that neither of these limitations are not met by the sheep plasma study of Dr. Eschbach.[116] Roche also failed to show that the EPO in sheep plasma was structurally the same as human erythropoietin as claimed in the '933 Patent.

Claims 11 and 14 of the '933 Patent are also limited to methods of treatment for kidney dialysis patients. The sheep plasma studies did not treat kidney dialysis patients and so this limitation of these claims is also not met.

2. The Human Plasma Study is Not Prior Art

The Court ruled at trial that the Eschbach article disclosing the human plasma study was not prior art, and so could not be entered into evidence.[117] Roche presented the human plasma study as Section 102(g) prior art, but Roche did not make the necessary showing for the plasma study to be Section 102(g) prior art as a matter of law.

To use the human plasma study as Section 102(g) prior art, Roche was obliged to establish by clear and convincing evidence that (1) another inventor who had not abandoned, suppressed or concealed, (2) reduced to practice the human plasma invention before the invention by Dr. Lin, or conceived of the human plasma invention before the invention by Dr. Lin followed by diligence to a reduction to practice, and (3) the prior reduction to practice or prior conception is supported by independent corroborating evidence.[118] Roche has not met this burden for the human plasma studies of Dr. Eschbach.

In addition, Dr. Spinowitz admitted that the human plasma studies of Dr. Eschbach did

[116] 9/12/07 Trial Tr. 874:11-19.

[117] 9/11/07 Trial Tr. 736:8 – 737:15.

[118] *See Sandt Tech.*, 264 F.3d at 1350.

not use an EPO that was purified from mammalian cells grown in culture,[119] and did not use an EPO that was the product of an exogenous EPO DNA sequence.[120] Claim 1 of the '422 requires that the human erythropoietin be purified from mammalian cells grown in culture, and the claims of the '933 Patent require that the glycoprotein be produced by mammalian cells from an exogenous DNA encoding human erythropoietin. Roche failed to present evidence showing that the human plasma EPO had the same structure as the human erythropoietin of claim 3. Thus, even if the human plasma study was prior art, which it is not, it could not anticipate Claim 1 of the '422 Patent, or Claims 9, 11, 12 and 14 of the '933 Patent.

D. THE HUMAN PLASMA STUDIES BY DR. ESSER DO NOT ANTICIPATE CLAIM 1 OF THE '422 PATENT, OR CLAIMS 9, 11, 12 AND 14 OF THE '933 PATENT

Dr. Spinowitz admitted at trial that the plasma EPO used by Dr. Essers was not purified from mammalian cells grown in culture[121], and was not the product of an exogenous EPO DNA.[122] Dr. Spinowitz also admitted that the plasma EPO used by Dr. Essers was not therapeutically effective because four out of five patients receiving the plasma had no change in reticulocytes, hemoglobin, or erythrocytes following administration of the human plasma.[123] The fifth patient showed an increase in reticulocytes but no change in hemoglobin or erythrocytes.[124] This change in one of three measured variables in one out of five patients administered human plasma does not show a therapeutic effect by clear and convincing evidence.[125] Because of this failure of proof the human plasma studies of Dr. Essers cannot

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[119] 9/12/07 Trial Tr. 860:25-861:23.

[120] 9/12/07 Trial Tr. 876:18-877:1.

[121] 9/12/07 Trial Tr. 860:25-861:12.

[122] 9/12/07 Trial Tr. 875:2-12; 876:18-877:1.

[123] 9/12/07 Trial Tr. 929:4-931:10.

[124] *Id.*

[125] *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F.Supp.2d 69, 111 (D.Mass. 2001).

anticipate Claim 1 of the '422 Patent.

Roche also failed to present evidence showing that the plasma EPO used by Dr. Essers had the same structure as the EPO which was the product of the claims of the '933 Patent.[126] Thus, for this reason and those cited above, the human plasma studies of Dr. Essers cannot anticipate Claims 9, 11, 12 and 14 of the '933 Patent.

E. THE HUMAN AND SHEEP PLASMA STUDIES COMBINED WITH THE uEPO STUDY DO NOT RENDER OBVIOUS CLAIM 1 OF THE '422, OR CLAIMS 9, 11, 12 AND 14 OF THE '933 PATENT

As stated above, none of these studies used a human EPO purified from mammalian cells grown in culture, and none of these references discloses a therapeutically effective amount of human erythropoietin. Thus, this combination of art cannot render obvious Claim 1 of the '422 Patent.

Also as stated above, Roche failed to prove that these studies demonstrated a therapeutically effective amount of human EPO, or that the EPO used in these studies was the product of an exogenous DNA encoding human EPO, *i.e.*, had the structure of a human erythropoietin made by the claims of the '933 Patent. Thus, this combination of art cannot render obvious Claims 9, 11, 12 and 14 of the '933 Patent.

F. CLAIM 7 OF THE '349 PATENT HAVING THE "VERTEBRATE CELLS" LIMITATION IS NOT INVALID FOR LACK OF WRITTEN DESCRIPTION OR ENABLEMENT

In Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11),[127] Roche alleged that claim 7 of the '349 patent is invalid due to lack of written description and enablement of the claim term "vertebrate cell" because the patent disclosure fails to enable

[126] *Hoechst*, 126 F.Supp. 2d at 111 ("Because the raw plasma was drawn from human blood . . . Dr. Esser's EPO product cannot be said to be non-naturally occurring * * * Moreover, like the tumor cell references, Dr. Esser's articles do not address glycosylation or molecular weight differences . . .").

[127] Filed 5/1/07.

and adequately describe the full scope of the claim.[128] In its Pre-Trial Brief,[129] Roche again alleged that the asserted claims of the '349 patent are not enabled and lack written description because the '349 patent purportedly describes only two cell lines, COS and CHO, and these are not allegedly representative of the entire group of "vertebrate cells" claimed.[130] As a consequence, Roche claims, one of ordinary skill in the art would not have been able to practice the full scope of claim 7 of the '349 patent without undue experimentation.[131]

Furthermore, Drs. Kadesch and Nunberg are Roche's only experts that opine on this issue in their 4/6/07 Expert Reports and neither testified during Roche's invalidity case at trial. Roche has no other expert that can opine on this issue at trial and, therefore, cannot present any evidence on this issue.

Because Roche has presented no evidence that the '349 patent disclosure fails to enable and adequately describe the full scope of this claim limitation or that practicing claim 7 would have required undue experimentation, Amgen is entitled to judgment as a matter of law that claim 7 of the '349 patent is adequately described and enabled with regard to the "vertebrate cells" claim limitation.

G. CLAIM 7 OF THE '349 PATENT HAVING THE LIMITATION OF "U OF ERYTHROPOIETIN PER 10^6 CELLS IN 48 HOURS AS DETERMINED BY RADIOIMMUNOASSAY" IS NOT INVALID FOR LACK OF ENABLEMENT[132]

Roche alleged in Dr. Flavell's 4th Supplemental Expert Report[133] that claim 7 of the '349

[128] Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11) at p. 12.

[129] Docket No. 919.

[130] *Id.* at pp. 50-52.

[131] *Id.*

[132] Amgen hereby renews its objection to the permissibility of Dr. Flavell's invalidity opinion based on the alleged non-enablement of radioimmunoassay claim limitation that was taken under advisement by the Court on September 24th. Roche has no other Section 112 challenge regarding this term.

patent is invalid for lack of enablement because the patent purportedly fails to disclose sufficient information to teach one of skill to correlate RIA results with biological assay results and further fails to instruct how to determine the number of Units of erythropoietin in an unknown sample having an unknown specific activity.[134]

Roche has presented no evidence that practicing claim 7 of the '349 patent would have required undue experimentation. Roche's expert, Dr. Flavell offered an enablement opinion based on the sole ground that, in his opinion, a person of skill in the art could have not known how to use radioimmunoassay because one would not be able to determine whether he was detecting a full length protein or a fragment of the protein. However, Dr. Flavell's opinion was unsupported by any evidence that a person of skill in the art would not have known how to perform an EPO RIA according to Claim 7 of the '349 Patent. Dr. Flavell ignored that both Dr. Lin and the prior art taugtht that one could easily account for the presence of fragments by use of a sizing column.[135]

In fact, Dr. Flavell did not rebut or reconcile his opinion with that of Roche's other experts. Dr. Lowe testified that "And the claim says radio immunoassay. It's a standard laboratory technique."[136] Roche's other expert on this point, Dr. Edward E. Harlow, testified at his June 20, 2007 deposition that one of skill in the art would have known how to perform a radioimmunoassay to detect the amount of EPO being produced by vertebrate cells:[137]

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[133] Filed 6/13/07.

[134] *Id.* at ¶¶ 55-67.

[135] Exhibit 1, Column 28, lines 33-50.

[136] Trial Tr. (9/6/07) 304:20-23.

[137] Amgen will be offering excerpts of Dr. Harlow's testimony into evidence as Roche admissions during Amgen's case in chief.

[p. 246:5-13]

Q. Now, radioimmunoassay techniques can be used to detect protein antigen if a suitable antibody is available, correct?
A. Yes.
Q. And **as of December 1983 as ordinarily skilled artisan would have known how to use a radioimmunoassay to measure the amount of protein antigen in a solution**, correct?
A. **That's correct**.

[p. 252:11-23]

Q. So at paragraph 43 you say that, "Some of these assay," and you include among these assays the in **vitro RIA referred to in the patents in suit, "allowed one to quickly follow and quantify the levels of EPO protein**." Do you see that in your report?
A. Yes.
Q. So is it your opinion that **one of ordinary skill in the art could have followed the RIA referred to in the patents in suit in order to quantify the levels of EPO protein** being produced by vertebrate cells?
A. **Yes**.

The conflicting opinions of Roche's experts do not meet Roche's burden to prove non-enablement by clear and convincing evidence. Consequently, Amgen is entitled to judgment as a matter of law that claim 7 of the '349 patent is enabled.

H. THE '422 AND '933 PATENT CLAIMS HAVING THE "PHARMACEUTICAL COMPOSITION" LIMITATION ARE NOT INAVLID FOR LACK OF ENABLEMENT

In Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11), Roche contends that claim 1 of the '422 patent invalid for lack of enablement and inadequate written description because there are no examples or general description of human clinical trials for using the claimed invention in human therapy in the patents-in-suit. [138]

Roche further alleged in Dr. Flavell's Expert Report[139] that none of the patents contain any disclosure which one of skill could use on their own to purify EPO protein in order to

[138] Roche's 5th Supplemental Response to Amgen's First Set of Interrogatories (Nos. 9-11) at pp. 18-19.

[139] Filed 4/6/07.

achieve the degree of homogenous, contaminant-free protein necessary to make a pharmaceutical composition.[140]

The testimony of Dr. Flavell offered by Roche on these issues were cursory and unsupported, the sum total of which is set forth in four pages of the rough transcript from today's testimony.[141] The substance in this testimony is even less weighty. Dr. Flavell's opinion was directed only to his opinion that the actual material produced in Example 10 was never administered to humans and could not be given to humans, without explanation or support.[142]Because Roche has failed to carry its burden of establishing lack of enablement by clear and convincing evidence, Amgen is entitled to judgment as a matter of law that claim 1 of the '422 patent and claims of the '933 patent (claims 9, 11, 12, and 14) are enabled.

I. DR. LIN'S SPECIFICATION ADEQUATELY DESCRIBES AND MAKES DEFINITE "HUMAN ERYTHROPOIETIN"

Dr. Flavell was the sole witness offered by Roche to meet its burden to prove by clear and convincing evidence that the term "human erythropoietin," as construed by the Court was indefinite or not described. Dr. Flavell's testimony was not directed to either the asserted claims of the '698 or '868 patent, or '933 claim 14.

As to the claims of the remaining '933 claims, and '422 claim 1 (and improperly to '349 claim 7), Dr. Flavell's testimony was limited to his opinion that the Court's construction ***must*** mean 165 amino acids and because Dr. Lin did not literally describe that product, it was both

[140] *Id.* at ¶¶ 54-57. Dr. Flavell's opinion regarding the non-enablement of purification of a "pharmaceutical composition" relate to '933 claims 9, 11, 12, and 14, and '422 claim 1.

[141] *See*, 9/24/07 Rough Tr. at 103:20-107:24.

[142] *Id.* Dr. Flavell's passing reference to the Lai Patent, U.S. Patent No. 4,667,016 (a patent that was never entered into evidence) does not satisfy the "clear and convincing" burden placed on Roche. The '016 patent, related to Amgen's commercial process for making its EPOGEN product, has no bearing on whether Dr. Lin's claims are enabled.

inadequately described and indefinite.[143] This testimony is insufficient:

- Dr. Flavell was applying his own construction to render his opinion.
- Dr. Flavell conflates the description and definiteness requirements and founds both his opinions on his single conclusion that "human erythropoietin" must mean a 165 amino acid molecule.
- Dr. Flavell acknowledged in his direct examination that one of skill in the art now knows EPO to be a 165 amino acid product[144] and that this is the product that Amgen makes and sells as EPOGEN.[145]
- In numerous places in the patent specification, particularly in Example 10, Dr. Lin describes his EPO product as "human erythropoietin."
- The Court has already held on summary judgment that Roche infringes '422 claim 1 including the "human EPO" limitation of the claim indicating that the claim term is not indefinite.

VI. CONCLUSION

For the reasons stated, Amgen respectfully requests that its motion for Judgment as a Matter of Law pursuant to Fed. R. Civ. P. 50(a) be granted.

[143] In a throw-away sentence, Dr. Flavell offered the opinion that "allelic variant" could include numerous EPOs but did not support this opinion with any evidence that such multitude actually exists or that one of ordinary skill in the art would be confused about what "human erythropoietin" is.

[144] 9/24/07 Rough Tr. at 99:20-25.

[145] 9/5/07 Tr. at 116 (Roche's counsel acknowledging that EPOGEN is a 165 amino acid product). *Regents of the Univ. of New Mexico v. Knight*, 321 F.3d 1111 (Fed. Cir. 2003); *Kennecott Corp. v. Kyocera*, 835 F.2d 1419 (Fed. Cir. 1987)

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Respectfully Submitted,

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