IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE Ltd, a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN-LA ROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No. 05-12237 WGY U.S. District Judge Young

SUPPLEMENTAL DIRECTED VERDICT OPPOSITION IN RESPONSE TO AMGEN'S SEPTEMBER 24 ARGUMENT REGARDING THE OBVIOUSNESS OF CLAIMS 11 AND 14 OF THE '933 PATENT

During the September 24 directed verdict hearing, Amgen cavalierly dismissed Roche's defense of obviousness as to claims 11 and 14 of the '933 patent as "low hanging fruit." In fact, as shown below, Roche has presented clear and convincing evidence sufficient for a reasonable jury to conclude that claims 11 and 14 of the '933 patent are invalid as anticipated under 35 U.S.C. § 102 and as obvious under 35 U.S.C. § 103.

Aside from the fact that claims 11 and 14 depend from claims that claim pharmaceutical composition differently, claims 11 and 14 are identical: "A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 [or claim 12] in an amount effective to increase the hematocrit level of said patient." (TRX 1, claims 11 and 14). Roche presented clear and convincing evidence, including multiple prior art references and unrebutted expert testimony regarding the knowledge of one of skill in the art, showing that

treating kidney dialysis patients with a pharmaceutical composition comprising erythropoietin to increase hematocrit was well-known in the art prior to 1983-1984. That evidence renders claims 11 and 14 obvious. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 2007 WL 2615498, *4 (Fed. Cir. Sept. 12, 2007) (finding method of treatment claim to be obvious).

The 1984 Eschbach 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). Roche's expert Dr. Lowe explained that one of skill in the art would have understood that CRF (chronic renal failure) -- a condition known to affect humans -- means "that the kidneys have failed, they're unable to perform the filtration functions, and that means that the patients with CRF must be on dialysis." (Lowe 299:1-4, 299:18). This was well-known. (*See* Lowe 299:24-300:1). Dr. Lowe's testimony stands unchallenged. Therefore, each limitation of Amgen's asserted method claims is expressly found in the prior art, leading to the inescapable conclusion that one of ordinary skill would, at the time of the "invention, " have been motivated to make and administer a pharmaceutical composition precisely as set forth in the asserted claims. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007) ("[a] person of ordinary skill is also a person of ordinary creativity" who uses "common sense" to solve problems in light of the prior art).

Roche's expert Dr. Spinowitz also testified without contradiction by Amgen that the

Baron-Goldwasser clinical study teaches the administration of a pharmaceutical composition comprising human erythropoietin to patients with CRF on dialysis. (Spinowitz 705:20-706:1, 769:11-15). Dr. Baron (who testified by deposition) corroborated Dr. Spinowitz's testimony and opinions. 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).[1]

Finally, 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. (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 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 suitable to treat CRF

[1] Aside from providing clear and convincing evidence of obviousness, sufficient evidence exists for a reasonable jury to also conclude that the Baron-Goldwasser clinical study anticipates claims 11 and 14 of the '933 patent under § 102(a) and § 102(b). 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).

patients and increase hematocrit. (Spinowitz 771:23-25).

The fact that hematocrit measurements were obtained from sheep and hamsters in the prior art rather than humans is of no moment. Indeed, Roche presented clear evidence to the jury that Dr. Baron did observe an increase in hematocrit in human patients participating in the Baron-Goldwasser clinical study. The jury is free to credit that evidence and the opinions of Roche's experts based on that evidence. *See United States v. Nishnianidze*, 342 F.3d 6, 14 (1st Cir. 2003) ("the jury's duty is to assess credibility, and it may accept or reject, in whole or in part, any testimony"). Furthermore, the prior art need not show actual administration in human kidney dialysis patients. As unrebutted testimony and documentary evidence has shown, one of skill in the art in 1983-1984 would have recognized that a pharmaceutical composition containing EPO would work to raise hematocrit. *In re Vaeck*, 947 F.2d 488, 492 (Fed. Cir. 1991) ("[t]he legal conclusion of obviousness does not require absolute certainty, ... but only a reasonable expectation of success"). Also, as a matter of patent law, *in vivo* testing in animal models can demonstrate that a pharmaceutical composition will work for its intended purpose. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (tests on humans are not required to show predictable success in treating humans). Indeed, Lin's specification -- which Amgen argues supports these same method of treatment claims -- relies solely on testing in mice with isolated (but unpurified) human EPO (TRX 1, col. 28:13-27)[2] to show that EPO will raise increase the hematocrit in a kidney dialysis patient.

In accordance with the substantial documentary evidence presented by Roche, and in accordance with the opinions expressed by Drs. Lowe, Spinowitz and Bertozzi, (*see* Lowe

[2] The Lin specification teaches that the mice are treated with "cell conditioned media from CHO cells," not EPO purified from the cell conditioned media.

299:21-300:1, 300:23-301:1; Spinowitz 768:25-769:10, 779:4-9, 801:11-802:1; Bertozzi 1053:14-1054:16), a reasonable jury could conclude that Roche has, by clear and convincing evidence, established the invalidity of '933 claims 11 and 14 due to obviousness and anticipation.

DATED: September 25, 2007

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

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CERTIFICATE OF SERVICE

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

/s/ Thomas F. Fleming
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