UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN'S RESPONSE TO VARIOUS FILINGS BY ROCHE (DOCKET NOS. 1232, 1291, 1315, 1332, 1343) REGARDING DATE OF INVENTION

I. INTRODUCTION

Attempting to assert that the belated activities of Dr. Fritsch (Trial Exhibits 2012.164, 2084, and 2090) and Dr. Eschbach (Trial Exhibit 20) somehow constitute ***prior*** art under 35 U.S.C. § 102(g)(2),[1] Roche presses the Court to instruct the jury that Dr. Lin made his inventions as of the filing date of his last patent application: November 30, 1984.[2] While ignoring that Dr. Lin's and Dr. Fritsch's dates of relevant activities have been judicially established, Roche asserts that Amgen's only evidence of invention dates for the claims-in-suit is Dr. Lin's testimony standing alone without any corroborating evidence. But the evidence of record establishing Dr. Lin's invention dates is much more than just Dr. Lin's testimony. Dr. Lin's priority patent filings of December 1983 (Trial Ex. 2014) and February 1984 (Trial Ex. 2015) disclose the cloning of the human EPO DNA and the production of human EPO in mammalian cells grown in culture. Dr. Browne's testimony and Amgen internal documents disclose the production of human EPO in several mammalian cell lines and the confirmation of *in vivo* biological activity by March — April 1984. Thus, the uncontroverted testimony and documentary evidence establish that Dr. Lin achieved his inventions long before the activities of Drs. Fritsch and Eschbach and certainly well ***before*** November 30, 1984.

II. LEGAL STANDARD

A patentee is entitled to offer evidence showing that the invention was made before the effective filing date of the application to overcome potentially invalidating art.[3] The patentee

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[1] § 102(g)(2) prohibits issuance of a patent only where the invention was made by another ***before*** the patentee invented the subject matter ("A person shall be entitled to a patent unless — … (2) ***before*** such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it."

[2] *See* D.I. No. 1343; *see also* D.I. Nos. 1232, 1291, 1332 [bench memoranda]; 1315 [JMOL].

[3] *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576-77 (Fed. Cir. 1996) (patentee "had the burden to offer evidence showing he invented the subject matter of his patent before the publication date

may establish an earlier invention date by demonstrating either (1) actual reduction to practice before the date of filing, or (2) conception before the date of filing followed by diligent reduction to practice.[4] A patentee may establish conception before the date of filing by showing that he or she had "a definite and permanent idea of the complete and operative invention" so that "only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation."[5] To establish a date of invention before the filing date, Amgen, the patentee, at most bears only a burden of production.[6] The burden of proving invalidity by clear and convincing evidence, in particular as to the activities of Drs. Fritsch and Eschbach, always remains with Roche — the patent challenger.[7]

III. ARGUMENT

A. AMGEN MORE THAN DISCHARGED ITS BURDEN OF PRODUCTION BY ITS UNCONTROVERTED EVIDENCE THAT DR. LIN ACCOMPLISHED *IN VIVO* BIOLOGICALLY ACTIVE HUMAN EPO IN MARCH 1984.

The evidence of record establishes that Dr. Lin demonstrated that he had produced recombinant human EPO having *in vivo* biological activity in mammalian cells grown in culture

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of the [alleged prior art]") (citing *Dir., Office of Workers' Comp. Programs v. Greenwich Collieries*, 114 S. Ct. 2251, 2255-57 (1994) (discussing burden of proof and burden of persuasion)).

[4] *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001) ("To antedate (or establish priority) of an invention, a party must show either an earlier reduction to practice, or an earlier conception followed by a diligent reduction to practice.").

[5] *Burroughs Wellcome Co. v. Barr Labs.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994).

[6] *Loral Fairchild Corp. v. Matsushita Elec. Indus. Co.*, 266 F.3d 1358, 1361 (Fed. Cir. 2001) (stating that patentee "would bear a burden of production to present evidence of its asserted actual reduction to practice prior to the filing date of its patent application").

[7] *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60 (Fed. Cir. 2007) ("'The presumption [of validity] remains intact and [the burden of proof] remains on the challenger throughout the litigation, and the clear and convincing standard does not change.'" (quoting *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed. Cir. 1986))).

in March 1984.[8] As the Court will recall, Dr. Browne testified that in March 1984, Dr. Lin's team achieved expression of human EPO from COS cells and proved it to be *in vivo* biologically active.[9] Dr. Browne's testimony is corroborated by EPO Project Team Meeting Minutes from March 27, 1984 (Trial Exhibit 30), which memorialize that the COS cell expressed human EPO was shown to be active in the *in vivo* assay.[10] Dr. Lin testified that in May 1984 his team achieved expression of human EPO from CHO cells and proved that man-made EPO to be *in vivo* biologically active.[11] Dr. Browne testified further about the amplification of the EPO DNA in CHO cells[12] and the high level of EPO production achieved in CHO cells was reported in Trial Exhibit 32.[13]

Contrary to Roche's assertion, Amgen has more than discharged its burden of production. Indeed, Amgen's showing stands completely uncontroverted. Roche proffered no evidence, much less clear and convincing evidence, refuting that Dr. Lin accomplished his achievements in

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[8] The claims-at-issue are not directed to an isolated and purified DNA molecule, but instead are directed to an *in vivo* biologically active EPO glycoprotein product, the process of making that product, pharmaceutical compositions, and a method for treating patients. For that reason, this memorandum does not address in detail the date of invention for the DNA claims. The invention date of those DNA claims, however, was the subject of extensive litigation before the BPAI, District Courts, and Federal Circuit. Findings by those courts establish unequivocally that Dr. Lin cloned the EPO gene, and therefore invented the DNA claims, in October 1983. *Amgen Inc. v. Chugai Pharm. Co.*, 13 U.S.P.Q.2d 1737, 1748 (D. Mass. 1989), *aff'd*, 927 F.2d 1200, 1203 (Fed. Cir. 1991). Furthermore, Dr. Lin's testimony in the current litigation confirms an invention date of October 1983 for the DNA claims. 9/27/07 Trial Tr. 1688:24-1689:2. This is confirmed by his patent application filed in December 1983, Trial Ex. 2014, which describes the cloning of the human EPO DNA.

[9] 9/28/07 Trial Tr. 1924:20-1925:11.

[10] Trial Ex. 30 at 2.

[11] 9/27/07 Trial Tr. 1755:18-1756:11 ("Our goal was to make – our goal was to make the in vivo biological active molecules, and so we achieve the goals in May 19 – achieve the goal in May 1984."). Dr. Browne confirmed this in his testimony. 9/28/07 Trial Tr. 1937:7-1939:20.

[12] 9/28/07 Trial Tr. 1934:4-1935:9.

[13] The *in vivo* and RIA results were reported in Trial Ex. 32, minutes of a team meeting on

March and again in May 1984. Roche therefore has no basis for requesting that the jury be instructed that Dr. Lin made his inventions as of November 30, 1984.

Notably, given that both the Patent Office and the courts specifically examined the question of when Dr. Lin achieved his accomplishments, it was particularly incumbent upon Roche to present evidence that was not only clear and convincing but also sufficient to overcome a heightened burden of proof.[14] In *Amgen v. Chugai*, Judge Saris detailed each step carried out by Dr. Lin and his team in developing the inventions of the claims-in-suit.[15] Judge Saris' decision presented a chronology of Dr. Lin's experiments, including the expression of an *in vivo* biologically active EPO product in COS cells in March 1984 and in CHO cells in May 1984.[16] Every one of those findings were upheld by the Federal Circuit.[17] Subsequently, Judge Saris' opinion was sent to the Patent Office, where it was considered and referenced by the examiner on multiple occasions during the examination of the applications leading to the patents-in-suit.[18] The Board of Patent Appeals and Interferences also relied on that decision in determining that

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August 22, 1984.

[14] *See Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990) (discussing heightened standard where evidence was previously considered by the PTO examiner during prosecution); s*ee also American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (same).

[15] 13 U.S.P.Q.2d 1737, 1746-50 (D. Mass. 1989).

[16] *Id.* at 1748-49.

[17] 927 F.2d 1200, 1203 (Fed. Cir. 1991).

[18] *See, e.g.*, Trial Exs. 2011.292, 2011.322-23, 2011.339, 2011.455, 2012.754, 2012.908, 2012.1040, and 2012.1044. The District Court decision in *Amgen v. Chugai* was originally part of the file history as indicated by an Amendment submitted to the Patent Office on January 10, 1990 ("The Applicant submits that any suspension of prosecution or declaration of an interference would be improper in view of the entire record now before the Patent Office, in particular the new evidence, including the priority determination, in the decision rendered by the United States District Court for the District of Massachusetts in *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd. and Genetics Institute, Inc.*, Civil Action No. 87-2617-Y, on December 11, 1989. A copy of that decision is attached hereto."). Trial Ex. 2011.292.

Dr. Lin was the prior inventor in the three *Fritsch v. Lin* interferences.[19] The Board's decision was put in evidence in this case by Roche.[20]

B. GIVEN THE DATES OF DR. LIN'S INVENTIONS, DRS. FRITSCH'S AND ESCHBACH'S ACTIVITIES ARE NOT "PRIOR" ART.

In its list of anticipatory art (D.I. 1340), Roche identifies the activities of Dr. Fritsch as set forth in Trial Exhibits 2012.164, 2084, and 2090 as providing evidence of anticipation under 35 U.S.C. § 102(g)(2). Roche argues (D.I. 1232) that Dr. Fritsch's conduct is prior art because "Dr. Fritsch isolated the EPO gene *before* the effective filing date of the patents-in-suit." Any suggestion that an alleged invention by another before the effective filing date of a patent, however, ignores the requirements of § 102(g). Section 102(g) explicitly refers to the "invention" date, not filing dates. For Dr. Fritsch's activities to constitute prior art, they must have occurred ***before*** Dr. Lin ***invented*** the claimed subject matter, not simply before he filed his application for patent.

None of the exhibits cited by Roche provide any evidence that Dr. Fritsch demonstrated that he had achieved the production of *in vivo* biologically active human EPO in mammalian cells ***before*** Dr. Lin. Indeed, Dr. Fritsch's deposition testimony claims that he first cloned a DNA encoding human EPO in July 1984, expressed EPO in COS cells sometime in September 1984 and CHO cells at some unspecified time.[21] In fact, Roche failed to provide any proof of the production of *in vivo* biologically active human EPO. Trial Exhibits 2084, 2012.164 and 2090 add nothing more to this showing. In sharp contrast, Amgen showed on clear evidence that Dr. Lin had isolated the DNA encoding human EPO by October 1983 and had achieved the first ever

[19] *Fritsch v. Lin*, 21 U.S.P.Q.2d 1731, 1734 (B.P.A.I. 1991).

[20] Trial Ex. 2012.1040.

[21] 9/7/07 Trial Tr. 353:3-24; 356:22- 357:7; 360:19-21.

demonstration of *in vivo* biologically active human EPO produced by mammalian cells grown in culture in March 1984. Notably, this is the identical finding regarding the relative dates of Dr. Lin's and Dr. Fritsch's work that Judge Saris made, the Federal Circuit affirmed, and the Patent Office considered. Roche completely failed to meet its burden of proof that Dr. Fritsch's activities came before Dr. Lin's inventions.

In its list of anticipatory art (D.I. 1340), Roche identifies Dr. Eschbach's 1987 publication (Trial Exhibit 20) as support for its assertion that his single patient experiment anticipates '933 claims 9 and 12 under 35 U.S.C. §§ 102(g) or 102(a) or (b).[22] But Roche misrepresents that publication (Trial Exhibit 20) as it ***nowhere*** even mentions this experiment. What remains of Roche's evidence is Dr. Spinowitz's testimony. But Dr. Spinowitz admitted that the experiment itself (the two infusions) occurred in November 1984 and that he had no knowledge as to the date when Dr. Eschbach obtained the plasma.[23] Simply put, Roche utterly failed to prove by clear and convincing evidence that Dr. Eschbach's experiment occurred ***before*** Dr. Lin invented his claimed invention. Indeed, it would be a miscarriage of justice to deny Amgen's clear showing as to Dr. Lin's March 1984 accomplishment while, on the basis of Roche's utterly deficient showing, award Dr. Eschbach's activities the status of "prior" art.

IV. CONCLUSION

Based on Amgen's uncontroverted evidence and Roche's complete failure of proof, Roche is not entitled to have the jury instructed that the date of Dr. Lin's inventions is November 30, 1984. Moreover, given that Dr. Fritsch's and Dr. Eschbach's activities cannot possibly

[22] D.I. 1315 at page 14; D.I. 1340 at page 3.

[23] 9/11/07 Trial Tr. 748:19-22; 9/12/07 931:23-932:18.

predate Dr. Lin's inventions, such activities are not prior art and should not be allowed to go to the jury for any purpose, including the determination of anticipation or obviousness.

Dated: October 14, 2007

AMGEN INC.,

By its attorneys,

/s/ Michael R. Gottfried

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