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 INC.'S MEMORANDUM IN SUPPORT OF MOTION TO SHIFT BURDEN OF PROOF FOR '349 CLAIM 7 PURSUANT TO 35 U.S.C. § 295

During the course of discovery in this case, Roche failed to provide timely and fulsome discovery regarding its cell line and the custom cell culture medium that it uses for producing the recombinant human EPO in its accused peg-EPO product (MIRCERA). As a result, while Amgen has been able to establish that there is substantial likelihood that the EPO in Roche's MIRCERA product was made by the process of '349 claim 7, its ability to offer direct evidence of Roche's infringement has been prejudiced by Roche's acts, despite Amgen's reasonable efforts. Therefore, pursuant to 35 U.S.C. § 295, Amgen asks the Court to shift the burden to Roche to establish that the cells it uses in its process for making EPO are not "capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as measured by radioimmunoassay."

35 U.S.C. § 295 provides:

> In actions alleging infringement of a process patent based on the importation, sale, offered for sale, or use of a product which is made from a process patented in the United States, if the court finds
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> (1) that a substantial likelihood exists that the product was made by the patented process, and
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> (2) that the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable so to determine,
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> the product shall be presumed to have been so made, and the burden of establishing that the product was not made by the process shall be on the party asserting that it was not so made.

Here, both requirements of the statute have been satisfied, and this Court should therefore shift the burden of proof of non-infringement of '349 claim 7 to Roche. [1]

First, Amgen has presented substantial evidence establishing that the recombinant human EPO in MIRCERA is made by the process of claim 7 of the '349 patent. Roche's admissions in its BLA,[2] as explained at trial by Dr. Lodish,[3] establish that Roche produces recombinant human EPO by culturing, under suitable nutrient conditions, vertebrate cells comprising non-human DNA sequences controlling the transcription of DNA encoding human erythropoietin, which cells are capable of producing in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.

Second, Amgen made a reasonable effort to determine the process actually used by Roche to produce its product. Specifically, Amgen sought samples of Roche's cells so that Amgen could grow the cells in accordance with Roche's instructions and cell culture conditions,

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[1] *Nutrinova Nutrition Specialties & Food Ingredients GmbH v. ITC*, 224 F.3d 1356, 1359 (Fed. Cir. 2000).

[2] Trial Ex. 52 at ITC-R-BLA-00004667, 4722, 5073, 5581

[3] Trial Transcript, Oct. 4, 2007, 2439:21–2457:10.

and then measure the EPO production rate using radioimmunoassay as specified in '349 claim 1. Roche, however, delayed and obstructed those efforts.

Although Amgen requested Roche's cells in its initial discovery requests in October 2006, Roche refused to produce its cells until almost the close of the fact discovery period in March 2007, forcing Amgen to bring a motion to compel (Docket No. 222), which was granted, and a subsequent motion to enforce its motion to compel (Docket No. 293), which was also granted.

When Roche finally produced its cells, Amgen's expert witness who was to grow the cells, Dr. Richard Kolodner, requested instructions regarding the cell culture medium that Roche is currently using to grow its cells for production of EPO. When Roche responded with the recipe for the custom cell culture medium it currently uses, Dr. Kolodner recognized that formulating that medium could not be accomplished in time (i) to grow the cells and (ii) for Dr. McLawhon to conduct the RIA testing on the cell culture medium conditioned by those cells before April 30, 2007, the date by which Drs. Kolodner and McLawhon had to submit their expert reports under this Court's Order of April 11, 2007.

When it was learned that the custom cell culture medium could not be formulated in time to comply with the Court's deadline for expert reports, Amgen asked Roche to supply some of its custom cell culture medium for use by Dr. Kolodner. Roche, through its trial counsel, agreed to supply its custom cell culture medium to Dr. Kolodner on April 19 and again on April 24.[4] Roche never did so (indeed, its trial counsel simply ignored Amgen's follow-up inquiries).

[4] *See* Exhs. 1 (email exchanges between P. Carson and K. Flowers between April 19, 2007 and May 4, 2007) and 2 (Carson letter to Flowers dated April 19, 2007) to Declaration of Cullen N. Pendleton. In Support of Amgen's Bench Memorandum Regarding Roche's Burden of Proof Pursuant to 35 U.S.C. § 295.

Consequently, although Amgen made a reasonable effort to determine the rate of EPO production for Roche's cells in the custom cell culture medium that Roche uses in its manufacturing process, Amgen was effectively "unable so to determine" because Roche refused to timely supply the both the cells and the custom cell culture medium that Roche uses to make that product. As a result, Dr. Kolodner was unable to grow Roche's cells in the identical culture medium used by Roche in its manufacturing process in Germany, and instead Dr. Kolodner was forced to attempt to re-create the proprietary cell culture medium used by Roche.[5] Using this re-created cell culture medium, Amgen's experts grew the cells, performed the radioimmunoassay test, and determined that Roche's cells were capable of producing 1377 units of EPO per 10^6 cells per 48 hours – well in excess of the 100 units required by '349 claim 1.[6]

While Amgen's experts believed that the small difference in culture conditions would not significantly affect the results,[7] Roche has made clear that it contests that position. In particular, Roche's expert, Dr. Richard Flavell, submitted an expert report in this case identifying an array of critiques of Amgen's radioimmunoassay tests on Roche's cells.[8] According to Dr. Flavell, "because Amgen's tests did not replicate the exact conditions employed by Roche, these tests cannot provide evidence that Roche practiced the process of Claim 7."[9] Furthermore, Roche has

[5] Expert Statement of Richard D. Kolodner, Ph.D. at ¶¶ 12-13

[6] Expert Report of Ronald W. McLawhon, Ph.D. at ¶ 32.

[7] Expert Report of Ronald W. McLawhon, Ph.D. at ¶ 24; Lodish Second Supplemental Report at ¶¶ 78-80.

[8] 6/13/07 Fourth Expert Statement of Richard A. Flavell, Ph.D. at ¶¶ 5-67.

[9] *Id.* at ¶ 8.

moved to preclude Amgen from offering testimonial or documentary evidence of its test data on the grounds that the experiments were not the product of reliable principles and methods.[10]

Of course, Roche has possession of its cells, cell culture medium, commercial scale bioreactor, and purification process at its manufacturing facility in Germany. Despite this fact, Roche has never produced any radioimmunoassay test results of its own which would contradict the data reported by Amgen's experts.

Although Amgen believes the evidence of record is more than sufficient to support a finding of literal infringement of '349 claim 7, Roche, not Amgen, should bear the consequences of any deficiency caused by Roche's gamesmanship regarding the production of its cells and the custom cell culture medium that Roche uses to grow those cells. "35 U.S.C. § 295 provides the trial court with a potent weapon to use against a non-cooperative defendant," and "a patentee has every right to urge the court to apply the provision when circumstances warrant it."[11] The Court's employment of that provision is required by the facts in this case. Accordingly, the Court should presume that the EPO product in MIRCERA is produced by the process of '349 claim 7, and Roche should bear the burden of proving that its EPO product is not the product of the process of '349 claim 7.

[10] Docket No. 1297, Roche's *Motion in Limine* to Preclude Amgen from Proffering Testimonial or Documentary Evidence Concerning Infringement Testing at 1.

[11] *Nutrinova*, 224 F.3d at 1360.

Dated: October 10, 2007

AMGEN INC.,
By its attorneys,

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