Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 821 Att. 1

EXHIBIT A

Statements Demonstrating That Issues 1-2 Are Subject to Issue Preclusion

Statements Supporting Issue 1

Recombinant erythropoietin cannot be distinguished from urinary erythropoietin on the basis of glycosylation.

1. "[T]wo uEPO [urinary EPO] preparations produced from the same batch of starting materials could nevertheless have different glycosylation patterns." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1340-41 (Fed. Cir. 2003).

2. "[A] skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 129 (D. Mass. 2001).

3. "By definition, one must know what the glycosylation of uEPO is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO. In its discussion characterizing recombinant glycoprotein products, the specification of the '933 patent does not direct those of ordinary skill in the art to a standard by which the appropriate comparison can be made." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1341 (Fed. Cir. 2003)

4. The reference Miyake, et al., Purification of Human Erythropoietin, J. Bio. Chem. 252, 5558, 5562 (1977) provides a method of purification, but does not suggest

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uniformity of glycosylation of the human uEPO studied. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1341 (Fed. Cir. 2003).

5. "Although the patent specification [of the patents-in-suit] refers to different urinary EPO preparations and methods for purifying urinary EPO, including the methods of Miyake et al. and Yanagawa et al., in the portion of the patent specification describing glycosylation experiments with recombinant and urinary EPO products, no specific information is provided regarding how to select a urinary EPO preparation for purposes of comparison. Furthermore, the patent does not specify which urinary EPO preparation ought be used as a standard in determining whether a particular EPO sample has glycosylation which differs from that of human urinary EPO. Though a skilled worker might be able to guess, such an artisan reading the '933 patent would not know which urinary erythropoietin preparation should be used as a standard in making the comparison described in the patent and called for by the claims." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 128 (D. Mass. 2001) (internal citations to evidence omitted).

6. "[T]he heterogeneity of EPO glycosylation is manifested by differences in the number, type, and arrangement of the individual monosaccharides that make up the carbohydrate chains." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 128 (D. Mass. 2001).

7. "In addition, the use of different methods of purifying erythropoietin results in different glycosylated erythropoietin populations." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 128 (D. Mass. 2001).

8. "Additional experiments conducted by Amgen scientists in 1984 showed that different urinary EPO preparations had different glycosylation." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 129 (D. Mass. 2001).

9. "Dr. Joan Egrie conducted a series of SDS-PAGE experiments comparing Lot 82 [urinary] EPO with a uEPO received from Dr. Eugene Goldwasser. Dr. Egrie compared the preparations side-by-side on the same gel and concluded that the Lot 82 and Goldwasser uEPO samples migrated differently on SDS-PAGE, with the Lot 82 material having a higher molecular weight. After performing additional tests before and after treatment with enzymes effecting deglycosylation, she also concluded that this difference in migration was due to differences in glycosylation. In particular, the Lot 82 and Goldwasser uEPO migrated differently before enzymatic treatment, and the two preparations migrated the same after such treatment. These tests confirmed that the difference in apparent molecular weight between Lot 82 [uEPO] and Goldwasser uEPO was caused by differences in glycosylation. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 129 (D. Mass. 2001) (internal citations to evidence omitted).

10. "Dr. Egrie came to the same conclusion when she compared a commercially available urinary EPO from Alpha-Therapeutics to Goldwasser uEPO." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 129 (D. Mass. 2001) (internal citations to evidence omitted).

11. "Dr. Egrie's various SDS-PAGE experiments reveal that different uEPOs have varying glycosylation." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 129 (D. Mass. 2001) (internal citations to evidence omitted).

12. "[T]he molecular weights of uEPOs vary as well." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 130 (D. Mass. 2001).

13. "Dr. Lin's disclosure [in the patents-in-suit] fails adequately to describe an EPO glycoprotein whose glycosylation differs from that of human urinary erythropoietin." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 155 (D. Mass. 2001).

14. "[T]he glycosylation of human urinary erythropoietin is a standardless standard"... [because] (1) the glycosylation of urinary erythropoietin has 'enormous heterogeneity'; (2) different purification techniques, several of which were known by one skilled in the art in 1984, result in differing glycosylated erythropoietin populations; (3) despite referring to at least two purification methods, the patent does not identify which human urinary erythropoietin preparation ought be used as a standard, nor would a skilled person know which urinary EPO preparation should be used; and (4) different urinary erythropoietin samples have different glycosylation. As a result, making comparisons between the glycosylation of recombinant EPO and that of human urinary EPO is virtually impossible." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 155 (D. Mass. 2001).

15. Dr. Lin failed to disclose in the patents-in-suit which of the varying urinary EPO preparations should be used as a standard for the glycosylation of natural EPO. "[O]ne of ordinary skill in the art as of 1984 would not be able to guess the appropriate EPO preparation. As a result, the patent fails to convey to one of ordinary skill in the art as of 1984 that Dr. Lin invented an erythropoietin glycoprotein product having

glycosylation which differs from that of human urinary erythropoietin." *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 155 (D. Mass. 2001).

16. "Although the language [of the '933 patent] contemplates that a competitor concerned with infringing the '933 patent can empirically determine whether its product's glycosylation differs from the glycosylation of human urinary erythropoietin, a definitive comparison is rendered impossible by the fact that human urinary erythropoietin itself varies significantly." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 156 (D. Mass. 2001).

17. "[B]ecause different urinary erythropoietin preparations vary in their glycosylation, and because neither the ['933] patent nor the prior art provides clear guidance as to which human urinary EPO standard ought be used, one of ordinary skill in the art would be unable to determine whether a particular erythropoietin has gylcosylation which differs from that of human urinary erythropoietin. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*,126 F. Supp.2d 69, 156 (D. Mass. 2001) (citations to evidence omitted).

18. "Dr. Lin's specification falters, ..., because it fails to enable one of ordinary skill in the art to compare the glycoyslation of the recombinant EPO product with that of human urinary erythropoietin." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp.2d 69, 165 (D. Mass. 2001).

Statements Supporting Issue 2

The claims of the patents-in-suit do not cover analogs beyond the handful disclosed in the specification.

19. "Details for preparing only a few EPO analog genes are disclosed" in the patents-in-suit. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)

20. "There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213-14 (Fed. Cir. 1991).

21. "Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, ... more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1214 (Fed. Cir. 1991).

22. "Amgen has engaged in an EPO analog program headed by Dr. Steven Elliott, who has a PhD from the University of California at Irvine in molecular biology and biochemistry, and began work at Amgen in 1983." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *56 (D. Mass. Dec. 11, 1989).

23. "Over 3,600 different analogs can be made by substituting at only a single amino acid position; and over a million different analogs can be made by substituting three amino acids." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *56 (D. Mass. Dec. 11, 1989) (internal citations to evidence omitted).

24. "Dr. Elliott said that Amgen had not measured all of the biological properties of the analogs he had made, and he did not know whether the analogs had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake. Dr. Elliott did not know if any of the plasmids described in the [patents-in-suit] had this biological property." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *56 (D. Mass. Dec. 11, 1989) (internal citations to evidence omitted).

25. "In April, 1989, Dr. Goldwasser testified concerning his work in an ongoing study funded by the National Institutes of Health to modify some of the amino acids in the intact EPO structure to see the result of those modifications on biological activity sites." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *57 (D. Mass. Dec. 11, 1989) (internal citations to evidence omitted).

26. By 1989 scientists had not yet sorted out which particular amino acid residue is required for biological activity in EPO, and the data was incomplete. By 1989 one would not know the effect of reagants on certain amino acid residues without empirical study because "[t]here is no theory that tells us what to look for." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *57 (D. Mass. Dec. 11, 1989) (internal citations to evidence omitted).

27. After five years of experimentation, as of 1989 Amgen was still unable to specify which EPO analogs have the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, Civ. A. No. 87-2617-Y, 1989 WL 169006 at *57 (D. Mass. Dec. 11, 1989) (internal citations to evidence omitted).

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