IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE, LTD., ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE, INC. Defendants.	Civil Action No. 05 CV 12237 WGY

DECLARATION OF DR. SVEN-MICHAEL CORDS IN SUPPORT OF ROCHE'S OPPOSITION TO AMGEN'S MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF '422 CLAIM 1, '933 CLAIM 4, AND '698 CLAIM 6

I, Sven-Michael Cords, hereby declare under penalty of perjury that:

1. I am currently Project Manager and Study Director at Bioassay GmbH in Gerlingen, Germany. I have worked for Bioassay GmbH in this position since 2006. I am responsible for the supervision and conduction of bioassays for pharmaceutical quality control in accordance with the European Pharmacopoeia and the supervision of bioassay development and business development. The Bioassay GmbH labs are located in Ludwigshafen and in Heidelberg, both of which have animal testing facilities. Currently, ten scientists are employed at Bioassay GmbH laboratories.

2. Before joining Bioassay GmbH, I worked for five years on different animal models during my doctoral thesis and conducted post-doctoral work in cooperation with animal testing sites at university. I subsequently worked for six years at Biomet Merck in Darmstadt, Germany, as the research and development manager in the development of medical devices such as bone substitutes and

coated implant materials. In addition, I was responsible for production of Patient Matched Implants in accordance with GMP at Biomet-Merck in Darmstadt, Germany.

3. I received my MBA in 2006 from the Merck German Partnership program at Pforzheim University of Applied Science. My MBA Diploma Thesis was in *Evaluation of Outsourcing Attractiveness Factors in Biopharmaceutical Manufacturing with Focus on Analytical Services.* I also studied veterinary medicine from 1987-1993 at the Veterinary University of Hannover. In July 1993, I passed the third part of the veterinary exam and approbation. (See C.V. attached to this report as Exhibit 1). A list of my publications and presentations is attached to this report as Exhibit 2.

4. Since joining Bioassay GmbH in 2006, I have run bioassay tests as part of my daily activities at the laboratory in Ludwigshafen. I have tested approximately 1000 samples, measuring the biological activity of Erythropoietin-samples in the parallel line assay according to the European Pharmacopoeia**.**

5. I make this declaration based upon my own personal knowledge and company information.

6. I have been asked by counsel for Defendants[1] to describe certain tests I performed at Defendants' request relevant to this Court's determination of whether material differences exist between Roche's unique chemical compound, Mircera, and human erythropoietin as claimed by the six patents-in-suit.[2] These tests were performed under contract in Ludwigshafen, Germany, at the labs of Bioassay

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[1] F. Hoffmann-La Roche, Ltd., Roche Diagnostics GmbH, and Hoffmann-La Roche, Inc. (collectively "Roche").

[2] U.S. Patent Nos. 5,441,868 (the " '868 patent"), 5,547,933 (the " '933 patent"), 5,618,698 (the " '698 patent"), 5,621,080 (the " '080 patent"), 5,756,349 (the " '349 patent"), and 5,955,422 (the " '422 patent") (collectively "the Amgen patents").

Labor für biologische Analytik GmbH ("Bioassay GmbH"). All tests were performed under my direct supervision.

7. In the paragraphs below, I set forth a detailed description of the experiments performed and state that the analyses presented herein faithfully reflect experimental data observed, collected, or measured.

8. I have conducted an independent bioassay experiment with various Mircera and EPO samples and controls, as instructed by Defendants, using samples prepared and provided by Defendants. In performing the experiments, I have relied on my years of education, research, and experience using animal bioassays as model assays for human systems, and my wealth of experience performing bioassays on EPO samples as part of my regular duties at Bioassay GmbH according to contracts with other clients.

9. The protocol used in these experiments, a modified protocol of the Normomouse Bioassay, is a reliable system through which to measure the kinetic responses of Roche's erythropoietic stimulating agent, Mircera, on reticulocyte production in mice, just as it is a reliable system to measure the kinetic response of Epoetin beta on reticulocyte production in mice, and to present the differences in stimulatory effect observed with Mircera versus Epoetin beta with the samples tested. I have not been asked to provide an opinion as to the pharmacological and/or pharmacokinetic or pharmacodynamic differences between Mircera and recombinant human erythropoietin according to the claims of the Amgen patents.

10. Based on the results obtained, as shown in Figures 1, 2, and 3 below, it is my opinion that the bioassay used to generate the data in these figures is a reliable system through which to observe and measure the kinetic activity, namely, reticulocyte production over time, of Roche's Mircera product,

and that such results with Mircera can be compared to results obtained using the same bioassay performed with Epoetin beta (which I may refer to herein simply as EPO).

11. This conclusion is based upon an understanding of bioassay techniques studying erythropoietic stimulating agents (ESAs), and my reasoning for reaching this conclusion is set forth below.

I. BACKGROUND INFORMATION

A. Mircera

12. I understand that the Mircera drug substance is chemically synthesized by combining a reactive succinimidyl ester of methoxy PEG-succinimidyl butanoic acid with Epoetin beta at one or more free primary amino groups. I also understand that this reaction results in a molecule with a molecular weight of approximately 60 kDa. As discussed below, I conducted a bioassay demonstrating the kinetic effects in mice of the Mircera drug substance and Epoetin Beta, as indicated by production of reticulocytes over time.

B. Bioassays

13. I have specifically worked with bioassays involving biologically active erythropoietin using a bioassay that quantitatively counts reticulocyte production in the blood of mice over time, after treatment with samples of EPO. I am highly familiar with analytical methods for quality control in conducting bioassays, and Bioassay GmbH does not conduct such tests exclusively for Roche In fact, our company typically performs over 1000 such assays per year for our clients. Therefore, I am particularly suited for performing the modified version of the Normomouse Bioassay requested by the Defendants, the results of which are described in this report.

II. IN VIVO COMPARISON OF MIRCERA TO EPO

14. I conducted certain tests at the direction of Defendants using samples prepared and sent by Defendants, using a protocol designed by and received from Defendants. In particular, I conducted a bioassay with Mircera, deglycosylated Mircera, EPO and deglycosylated EPO samples, and appropriate controls. The experiment was designed and performed to evaluate the efficacy and reliability of using this particular bioassay for comparing the kinetic differences between the in vivo activity of Mircera and Epoetin beta, based on an increase in reticulocytes in the blood of mice over time, after treatment with the various samples and controls, and to generate useful data regarding the samples by which they can be compared. I provide below an overview of the protocol used, and a presentation of my observations and interpretation of the data collected.

A. Sample Preparation

15. The following seven samples were received from Defendants on March 26, 2007 for study in the bioassay experiment (with sample concentrations in parenthesis):

- Epoetin beta (8800 µg/mL)
- Epoetin beta mock-treated (240 µg/mL)
- Epoetin beta deglycosylated (100 µg/mL)
- Mircera (5900 µg/mL)
- Mircera mock-treated (130 µg/mL)
- Mircera deglycosylated (120 µg/mL)
- Control (0 µg/mL)

16. It is my understanding that the samples received and listed above were prepared by Markus Dembowski, of Roche Pharmaceuticals, Penzberg, Germany (see the Declaration of Markus Dembowski, attached to this report as Exhibit 4). I was not informed of how the samples were prepared, or what, exactly, the samples were, other than what is apparent from the brief descriptions and concentrations listed above.

17. After receiving the samples, all samples were diluted to a concentration of 200 ng/mL each in 1-3 dilution steps, depending on the starting concentration of the particular sample.

B. Test Procedure Protocol

18. In order to measure the *in vivo* responses to the various sample treatments in normal, healthy male $B_6D_2F_1$ mice, 7 weeks old, approximately 20g, reticulocyte counts per 30,000 cells were measured at 48, 72, 96, and 120 hours after treatment.

19. A total of 140 mice were used to conduct the bioassay. Twenty mice were treated and tested for each of the samples. Each group of twenty mice was divided into four subgroups of five mice per day over the course of four days.

20. The mice in the first six groups were each injected subcutaneously with 0.5 mL of the final solution, containing 100 ng of the respective samples: (1) EPO, (2) EPO K (mock-treated), (3) deglycosylated EPO, (4) Mircera, (5) Mircera K (mock-treated), and (6) deglycosylated Mircera; the seventh group, the control group, was injected subcutaneously with 0.5 mL of the vehicle solution only, which contained no test sample.

21. For each of these seven test groups, five different mice were bled on each of the four indicated days. Blood samples of 5 μL were drawn by puncture of the tail vein of each mouse.

22. The blood was then diluted so that 1 μL of blood was present in 1 mL of a 0.15-mM acridine orange staining solution. The staining time was 3-10 minutes. Reticulocyte count per 30,000 cells was determined for each mouse in the study by FACS-analysis at hours 48, 72, 96, and 120 in accordance with standard procedures using a Becton Dickinson FACScan flow cytometer with loader.

C. Results

23. Figure 1 below represents in table form the results generated by the bioassay protocol described above, including calculation of the mean, standard deviation, and relative standard deviation for each group.

Time [hrs]	Mouse	Epoetin beta			Mircera			Control
		Start material	mock treated	Deglyco-sylated	Start material	mock treated	Deglyco-sylated	vehicle
48	**1 value**	1066	834	498	963	1242	761	238
	2 value	937	895	465	924	800	786	344
	3 value	1084	960	388	1105	954	928	232
	4 value	1116	911	470	1126	1084	951	252
	5 value	1263	945	504	993	1045	712	413
	mean	**1093**	**909**	**465**	**1022**	**1025**	**828**	**296**
	SD	**117**	**49**	**46**	**89**	**163**	**106**	**80**
	RSD	**11**	**5**	**10**	**9**	**16**	**13**	**27**
72	**1 value**	1386	1430	555	2136	2048	1466	401
	2 value	1403	1189	641	2006	1921	1424	304
	3 value	1383	1460	341	1851	1730	1456	252
	4 value	1481	1209	346	2012	1760	1350	428
	5 value	1310	1225	524	2083	1800	1311	384
	mean	**1393**	**1303**	**481**	**2018**	**1852**	**1401**	**354**
	SD	**61**	**131**	**133**	**107**	**132**	**68**	**73**
	RSD	**4**	**10**	**28**	**5**	**7**	**5**	**21**
96	**1 value**	1285	797	459	3526	2149	839	341
	2 value	1258	745	333	2783	3015	1489	388
	3 value	1350	803	~~**1697**~~	3022	2360	1527	367
	4 value	1333	988	594	2957	2359	1170	325
	5 value	1070	949	344	2681	2406	1378	259
	mean	**1259**	**856**	**433**	**2994**	**2458**	**1281**	**336**
	SD	**112**	**106**	**122**	**327**	**327**	**283**	**49**
	RSD	**9**	**12**	**28**	**11**	**13**	**22**	**15**
120	**1 value**	482	392	326	3134	2754	667	401
	2 value	412	379	360	2644	3038	652	316
	3 value	343	381	437	3801	3168	475	794
	4 value	381	358	453	3125	2661	584	337
	5 value	440	404	282	3176	2279	570	349
	mean	**412**	**383**	**372**	**3176**	**2780**	**590**	**439**
	SD	**53**	**17**	**73**	**412**	**347**	**77**	**201**
	RSD	**13**	**4**	**20**	**13**	**12**	**13**	**46**

"value" = count of reticulocytes per 30,000 cells
Data 96 h: Value 3 EPO deglycosylated is found technical outlier (mouse) and eliminated

Figure 1.

24. One technical outlier was eliminated (Epoetin beta Deglycosylated, 3 value, 96 hours).

25. As Figure 1 demonstrates, the relative standard deviation of the reticulocyte counts for both Epoetin beta and Mircera throughout the study were very low and generally under 15% in those groups which showed a distinct value above the untreated control.

26. Figure 2 below shows a graph corresponding to the reticulocyte counts for each of the seven groups of mice measured at hours 48, 72, 96, and 120.

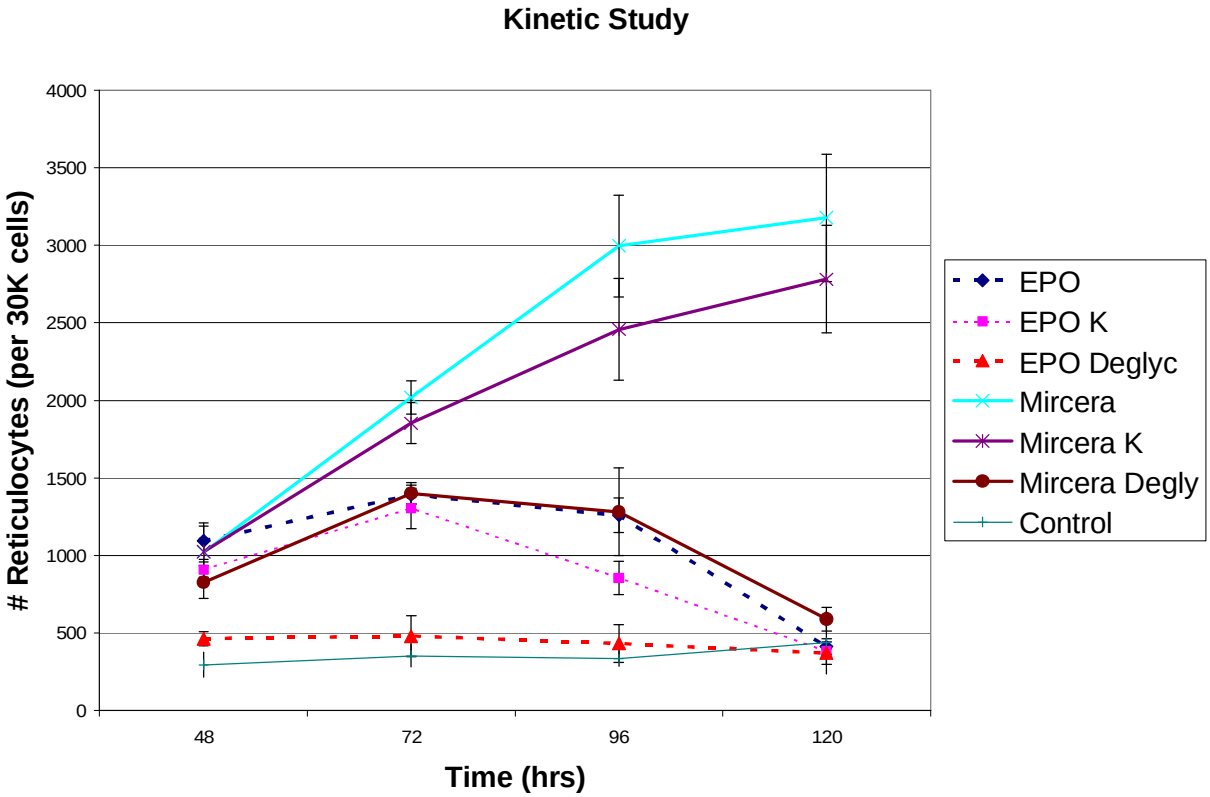

Figure 2.

27. As shown in Figure 2, mice treated with each variant of Mircera showed higher reticulocyte responses at 72, 96 and 120 h than those treated with the respective EPO variants. Furthermore, Mircera-treated and Mircera mock-treated mice showed a sustained increasing response through the first 120 h, whereas their respective EPO counterparts reached a maximum reticulocyte count at 72 h and thereafter showed decreased reticulocyte counts. Also, deglycosylated Mircera-treated

mice showed nearly identical reticulocyte counts at 72 h and 96 h compared to the number of reticulocytes observed for EPO-treated mice at 72 h and 96 h, and only slight differences in reticulocyte counts were observed between deglycosylated Mircera and EPO at 48 h and 120 h. Further, after 72 h deglycosylated EPO-treated mice showed similar reticulocyte counts as those from the control group (vehicle alone), i.e. no significantly detectable stimulation of reticulocyte production was observed.

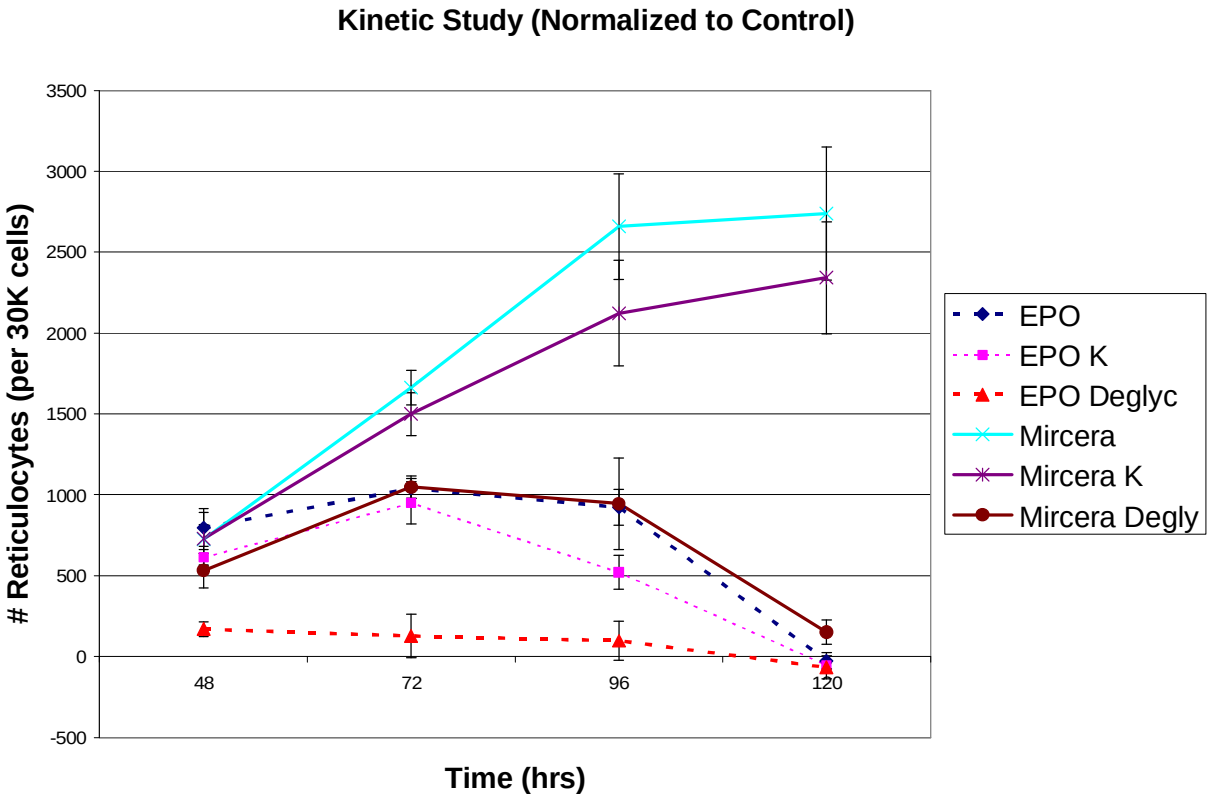

Figure 3.

28. Figure 3 above shows the data from Figure 2 normalized to the reticulocyte counts measured for the control (vehicle alone) mouse group. This graph emphasizes the difference in the response observed in EPO treated mice compared to that seen in Mircera-treated mice. Again, Mircera induced much stronger and prolonged erythropoietic responses, as indicated by reticulocyte counts/30,000 cells, over the 120-hour measurement span.

29. The above results indicate that this bioassay is a very reliable and accurate means by which to evaluate the in vivo kinetic responses induced by treatment with EPO or Mircera, as indicated by increase reticulocyte counts per 30,000 cells over time, and that comparison of the results obtained in this bioassay for these two molecules is possible.

30. The results of this procedure lead me to conclude that this bioassay is thus a reliable system through which to observe and compare the erythropoietic responses in mice to treatment with EPO or Mircera.

31. I hereby certify that the experimental results described herein faithfully represent my direct observations of each of the tests performed. I furthermore declare that all information so generated by me has been disclosed to both parties to the litigation in its entirety.

32. In light of the foregoing analysis, it is my expert opinion that the bioassay I conducted, which is a modified version of the Normomouse Bioassay, is a reliable and accurate assay to measure the in vivo kinetic responses in mice to EPO or Mircera, and that this assay may also be used to compare reticulocyte kinetic response to these compounds in mice.

33. The results of the experiments described in this declaration show that deglycosylated Micera (containing the active ingredient CERA) still retains a significant amount of its erythropoietic activity as compared to deglycosylated EPO. Given the significant erythropoietic activity demonstrated by N-deglycosylated Micera, these data strongly indicate that CERA is not an obligate glycoprotein.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: June 29, 2007

/s/ Sven Michael Cords
Dr. med. vet. Sven-Michael Cords, MBA

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) and paper copies will be sent to those indicated as non registered participants on the above referenced date.

/s/ Keith E. Toms

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