EXHIBIT 2

EXHIBIT G

Distinctions Between Claims of '008 Patent and Asserted Claims-in-Suit

'422 Claim 1

1. I understand that certain elements of '422 claim 1 have been interpreted by the Federal Circuit Court of Appeals.

2. There are several material distinctions between the claims of the '008 patent and '422 claim 1.

3. First, '422 claim 1 does not require isolated and purified EPO (or EPO analog) DNA, the key element of each '008 claim.

4. Second, '422 claim 1 is directed to a pharmaceutical composition, a concept absent from all of the '008 claims. "Pharmaceutical composition" implies a preparation of very high purity, free from containments that would raise a negative reaction in the patient. The '008 claims do not suggest that EPO should be used as a pharmaceutical composition, nor do they provide a reasonable expectation of success in making a human EPO pharmaceutical composition comprising EPO purified from mammalian cells grown in culture.

5. Third, '422 claim 1 requires that the claimed pharmaceutical composition be present in a "therapeutically effective amount." I understand that Amgen is currently appealing the Federal Circuit's interpretation of this term because it contends this Court's construction was proper. Regardless of which interpretation of this limitation applies, '422 claim 1 is not expressed in terms of a capability or a desire — it requires the tangible, concrete presence of a certain quality and quantity of pharmaceutically active human erythropoietin, which provides both of erythropoietin's in vivo biological activities (per the Federal Circuit) or the therapeutic activity of helping to heal or cure (per this Court). As described above, the '008 claims do not

suggest, teach, or provide a reasonable expectation of success for practicing this limitation.

6. Fourth, '422 claim 1 requires the presence of an appropriate "diluent adjuvant or carrier." This requirement is not suggested in any way by any of the '008 claims.

7. Fifth, '422 claim 1 requires that the human erythropoietin be "purified from mammalian cells grown in culture." This limitation establishes another difference from the claims of the '008 patent. The '008 claims do not recite or suggest purification of EPO. Indeed, "purified" requires significant amounts of high quality starting material. It was well known in 1983 that a threshold quantity of the starting material is necessary for purification. Moreover, this Court held in the HMR/TKT matter that prior art purification techniques were not applicable to purification of EPO from mammalian cells grown in culture: "the Court is persuaded that one of ordinary skill in the art could not have used the prior art purification methods to purify to substantial homogeneity the EPO produced in tumor cell cultures."[1] Nothing in the '008 claims requires or teaches a production level sufficient for purification, or a purification technique that would be successful for the purification of EPO from mammalian cells grown in culture.

8. In my opinion, these significant differences between '422 claim 1 and the '008 claims represent patentable distinctions and preclude a determination that '422 claim 1 is invalid for obviousness type double patenting over the '008 claims.

'080 Claims 3, 4, and 6

9. There are several material distinctions between the claims of the '008 patent and claims 3, 4, and 6 of the '080 patent.

10. First, unlike the '080 claims, the '008 claims do not claim a non-naturally occurring erythropoietin glycoprotein. In fact, no claim of the '008 Patent claims erythropoietin

[1] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 311 (D. Mass. 2004).

of any kind.

11. I understand that certain elements of the '080 claims have been interpreted by the Federal Circuit Court of Appeals. The Federal Circuit interpreted "non-naturally occurring" which is an element of each of '080 claims 3, 4, and 6, as follows:

> "As to the '080 patent, the 'non-naturally occurring' limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use negative limitations such as 'non-human' and 'non-natural' to avoid rejection under § 101. See *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 923, 18 USPQ2d 1677, 1680 (Fed. Cir. 1991). The district court arrived at a similar conclusion, *Amgen*, 126 F. Supp. 2d at 89, 57 USPQ2d at 1462-63, and TKT has not demonstrated any error in that conclusion. Similarly, the 'not isolated from human urine' limitation in claims 2 and 4 of the '080 patent simply requires that the claimed EPO, however made, be obtained from a source other than human urine. Each of these limitations only excludes human EPO from specific sources and does not restrict the claimed EPO to that produced from any particular source or by any particular method. In sum, claims 2, 3, and 4 of the '080 patent remain broadly drawn to the described 'erythropoietin glycoprotein' or 'pharmaceutical composition' produced by any method, or obtained from any source, other than those specifically excluded."[2]

12. Second, the '008 claims do not disclose the mature amino acid sequence of erythropoietin.

13. This Court and the Federal Circuit interpreted "the mature erythropoietin amino acid sequence of FIG. 6," which appears in all of the '080 claims, to require the entire 166 amino acid sequence for human EPO set out in Fig. 6 of Lin's patent, including arginine 166, which is cleaved off of EPO during processing by the cell: "the claimed glycoprotein must have -- at

[2] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003)

minimum -- all 166 amino acids shown in Figure 6."3

14. Third, as I have described above in the context of '422 claim 1, the '008 claims do not require, or provide a reasonable expectation of success in obtaining EPO "having the in vivo biological activity of causing bone marrow cells to increase production of reticuloytes and red blood cells."

15. Fourth, as I have described above in the context of '422 claim 1, the '008 claims do not suggest, teach, or provide a reasonable expectation of success in practicing an EPO pharmaceutical composition as required by '080 claim 4.

16. Fifth, the '008 claims do not suggest, teach, or provide a reasonable expectation of success in practicing a method of treating kidney dialysis patients by raising their hematocrit as required by '080 claim 6.

17. In my opinion, these significant differences between '080 claims 3, 4, and 6 and the '008 claims represent patentable distinctions and preclude a determination that '080 claims 3, 4, and 6 are invalid for obviousness type double patenting over the '008 claims.

'933 Claims 3, 7-9, and 11-12, and 14

18. There are several material distinctions between the claims of the claims of the '008 patent and claims 3, 7-9, and 11-14 of the '933 patent.

19. First, like the claims of the '080 patent, but unlike the '008 claims, all of the asserted claims of the '933 patent are either directed to a non-naturally occurring glycoprotein product, or a method of treatment involving administering same.

20. As set forth above, "non-naturally occurring" was addressed by the Federal Circuit in the context of the '080 claims. I know of no reason why this element would have a

[3] *Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1345 (Fed. Cir. 2003).

different meaning in the context of the '933 claims.

21. I understand that the term "effective for erythropoietin therapy has now been tentatively construed by the Court.

22. Second, and also like the claims of the '080 patent, all of the '933 claims are directed to a glycoprotein product "possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." As explained above, none of the claims of the '008 patent recite or provide a reasonable expectation of success in practicing such a limitation.

23. Third, and also like '422 claim 1 and '080 claim 4, '933 claims 9, 11, 12, and 13 require a pharmaceutical composition comprised of an EPO glycoprotein product, another element missing from the '008 claims. The significance of this limitation is described above in the context of '422 claim 1.

24. Fourth, '933 claims 11 and 14 require that when the claimed pharmaceutical composition is administered to kidney dialysis patients, it increases their hematocrit. There is no suggestion or teaching of this claim element in any of the '008 claims. Nor would the '008 claims, in light of the prior art, provide an ordinarily skilled artisan a reasonable expectation of success in achieving the claimed increase in hematocrit.

'868 Claims 1 and 2

25. '868 claim 1 recites a process for producing and isolating in vivo biologically active EPO glycoprotein in a mammalian host cell to which exogenous EPO DNA has been introduced. '868 claim 2 is a similar process performed using CHO host cells only. These claims have not been previously construed by any court.

26. As described just above, there are at least two material distinctions between the

claims of the ‘008 patent and claims 1 and 2 of the ‘868 patent.

27. First, the asserted claims of the ‘868 patent positively require that the product of the claimed process to have the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, while the ‘008 claims do not. The unexpected capacity to replicate the functional contribution of post-transitionslation modifications such as glycosylation is what makes the glycoprotein invention claimed in the ‘868 patent non-obvious over the DNA invention claimed in the ‘008 patent. It is one thing to have a DNA that will cause a cell to produce a glycoprotein; it is a very different thing to produce a glycoprotein that will have a desired in vivo activity.

28. Second, the ‘008 claims are to DNA products and host cell products, while ‘868 claims 1 and 2 are to processes for producing in vivo biologically active erythropoietin glycoproteins.

29. In my opinion, these significant differences between ‘868 claims 1 and 2 and the ‘008 claims represent patentable distinctions and preclude a determination that ‘868 claims 1 and 2 are invalid for obviousness type double patenting over the ‘008 claims.

698 claims 4-9

30. The asserted ‘698 claims recite processes for producing and isolating in vivo biologically active EPO glycoprotein in a vertebrate host cell with defined structural attributes.

31. Some of the claim terms of the ‘698 claims, including “vertebrate cells” (all ‘698 claims), “mammalian cells” (claim 9), and “operatively linked” (claims 4 and 5) were interpreted by the Court in the HMR/TKT matter.4

[4] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 83-90 (D. Mass. 2001) *aff’d in pertinent part* 314 F.3d (Fed. Cir.2003; *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 245-258 (D. Mass. 2004) *aff’d in pertinent part* 457 F.3d 1293, 1308 (Fed. Cir. 2006).

32. The asserted ‘698 claims are patently distinct from the ‘008 claims for at least the same reasons as the ‘868 claims. Moreover, there are several additional material distinctions between claims 4-9 of the ‘698 patent and the claims of the ‘008 patent.

33. First, none of the ‘698 claims require transfected isolated and purified EPO (or EPO analog) DNA, the key element of the ‘008 claims. As I explained above, if the ‘698 claims required transfection of purified and isolated EPO DNA, then TKT’s “gene-activated” EPO process would not have been found infringing by this Court and the Federal Circuit.

34. Second, ‘698 claim 4 recites the term “comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6.” There is no equivalent limitation in any ‘008 claim.

35. Third, ‘698 claim 5 recites the term “wherein said promoter DNA is viral promoter DNA.” There is no equivalent limitation in any ‘008 claim.

36. Fourth, ‘698 claim 6 recites the term “comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6.” There is no equivalent limitation in any ‘008 claim.

37. Fifth, ‘698 claim 7 recites the term “further comprise amplified marker gene DNA.” There is no equivalent limitation in any ‘008 claim.

38. Sixth, ‘698 claim 7 recites the term “wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.” There is no equivalent limitation in any ‘008 claim.