CLAIMS

1. A method of culturing heterologous protein-secreting mammalian cells in a cell culture supernatant wherein the cell culture supernatant is maintained at a pH that is set at X±0.05 wherein X has a value of from 7.15 to 7.20, with the proviso that the pH is set at greater than 7.10, wherein the cell density is $1.4x10^6$ to $2.8x10^6$ cells/ml.

2. A method according to Claim 1 wherein the pH is selected from 7.20±0.05, 7.20±0.03, 7.20±0.01, 7.20, 7.15±0.05, 7.15±0.03, 7.15±0.01 and 7.15.

3. The method of any preceding claim wherein the cell culture supernatant is buffered with bicarbonate.

4. The method of any preceding claim wherein the supernatant is sparged with air.

5. The method of any preceding claim wherein the heterologous protein is a blood protein.

6. The method of Claim 2 wherein the heterologous protein is Factor VIII.

7. The method of Claim 6 wherein the Factor VIII is co-expressed with von Willebrand Factor.

8. The method of any preceding claim wherein the concentration of Cu^{2+} in the cell culture supernatant is at least 5, 7, 10, 15 or 25 ppb.

9. A method according to Claim 2 wherein the heterologous protein is ADAMTS-13 or furin.

10. A method according to Claim 2 wherein the heterologous protein is Factor VII.

11. The method of any preceding claim wherein the mammalian cell is a rodent cell, such as a CHO cell or a BHK cell.

12. The method of any preceding claim wherein the culture is a batch culture.

13. The method of any of Claims 1 to 10 wherein the culture is a fed-batch culture.

14. The method of any of Claims 1 to 10 wherein the culture is a continuous culture, particularly a repeated batch, chemostat or turbidostat culture.

~~15. A method of culturing heterologous protein-secreting mammalian cells in a cell culture supernatant wherein the cell culture supernatant has a dissolved CO_2 concentration of 1 to 10%, wherein the cell density is from $1.4x10^6$ to $2.8x10^6$ cells/ml.~~

16. A method according to Claim 15 wherein the CO_2 concentration is either 4.0 to 9.0% or 5.5 to 8.5%.

17. The method of Claim 15 wherein the cell culture supernatant is maintained at a temperature that is set at X±0.9°C wherein X has a value of from 35.1 to 36.5, with the proviso that the temperature is set at less than 37°C.

18. A method according to Claim 17 wherein the temperature is selected from 36±0.9°C, 35.1±0.9°C, and 36.5±0.9°C.

19. The method of Claim 15 or 17 wherein the cell culture supernatant is maintained at a pH that is set at X±0.5 wherein X has a value of from 7.15 to 7.20, with the proviso that the pH is set at greater than 7.10.

20. The method of any preceding claim wherein the cell culture supernatant is buffered with bicarbonate.

21. The method of any preceding claim wherein the supernatant is sparged with air.

22. The method of any preceding claim wherein the heterologous protein is a blood protein.

23. The method of Claim 15 wherein the heterologous protein is Factor VIII.

24. The method of Claim 23 wherein the Factor VIII is co-expressed with von Willebrand Factor.

25. The method of any preceding claim wherein the concentration of Cu^{2+} in the cell culture supernatant is at least 5, 7, 10, 15 or 25 ppb.

26. A method according to Claim 15 wherein the heterologous protein is ADAMTS-13, furin or Factor VII.

27. The method of any preceding claim wherein the mammalian cell is a rodent cell, such as a CHO cell or a BHK cell.

28. The method of any preceding claim wherein the culture is a batch culture.

29. The method of any of Claims 15 to 26 wherein the culture is a fed-batch culture.

30. The method of any of Claims 15 to 26 wherein the culture is a continuous culture, particularly a repeated batch, chemostat or turbidostat culture.