the culture medium is not supplemented with animal products, such as serum, the medium may support only relatively low cell densities. This reduces the yield per volume of medium. However, it is desirable not to supplement the culture medium with animal products in order to reduce the risk of contamination with viruses and other transmissible agents. Animal-protein-free media for the production of FVIII are known from US 6 936 441 (Baxter AG), for example.

The present invention provides processes for producing blood proteins, including rFVIII, in which the yield is improved compared to processes known in the art.

SUMMARY ~~OF THE INVENTION~~

In one aspect, there is provided 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.

A first ~~aspect~~embodiment of the ~~invention~~disclosure provides a method of culturing heterologous protein-secreting mammalian cells in a cell culture supernatant 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.

A second ~~aspect~~embodiment of the ~~invention~~disclosure provides 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.

A third ~~aspect~~embodiment of the ~~invention~~disclosure provides a method of culturing heterologous protein-secreting mammalian cells in a cell culture supernatant wherein the cell *culture supernatant has a* CO_2 *concentration of* 1-10%.

A fourth ~~aspect~~embodiment of the ~~invention~~disclosure provides a method of continuous culture of FVIII-*secreting mammalian cells in a vessel comprising a cell culture supernatant* wherein the density of the cells in the cell culture supernatant is measured by an in-line sensor and the influx of fresh medium into the vessel is automatically controlled so as to maintain the density of the cells in a desired range.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

In the process of the first aspect of the invention, the cell culture supernatant in which the mammalian cells are cultured is maintained at a temperature that is set