collected the host cells and the expressed recombinant proteins remain in the retentate in the bioreactor and the permeate is substantially free of or has significantly less of either, wherein a harvest permeate is collected using a hollow fiber filter having a pore size or molecular weight cut off that does not retain the recombinant protein in the bioreactor wherein when the harvest permeate is collected the host cells are retained in the bioreactor and the expressed recombinant proteins pass into the permeate, the fresh cell culture medium is formulated with or supplemented to achieve at least 5g/L of a non-ionic block copolymer; wherein the null permeate is initially collected until a first predetermined parameter is reached, at which time the harvest permeate is collected for a predetermined time, the harvest permeate comprising the recombinant protein, this is followed by alternately collecting the null permeate until a second predetermined parameter is reached, then collecting the harvest permeate for a predetermined time, wherein the alternating collection of null permeate and harvest permeate continues until the cell culture is terminated, wherein the predetermined parameter is selected from time, viable cell density, packed cell volume, or titer. Also described herein is a method for an extended periodic harvest comprising establishing a cell culture by inoculating a bioreactor with mammalian cells expressing a recombinant protein, maintaining the cell culture by perfusing fresh cell culture medium into the bioreactor, passing the cell culture through a filter and collecting a permeate, wherein a null permeate is initially collected until a first predetermined parameter is reached, at which time a harvest permeate is collected for a predetermined time, this is followed by alternately collecting a null

CLAIMS

1. A method for an extended periodic harvest comprising

establishing a cell culture by inoculating a bioreactor with mammalian cells expressing a recombinant protein,

maintaining the cell culture by perfusing fresh cell culture medium into the bioreactor, passing the cell culture through a filter and collecting a permeate, wherein a null permeate is collected using a hollow fiber filter having a pore size or molecular weight cut off that retains the recombinant protein in the bioreactor wherein when the null permeate is collected the host cells and the expressed recombinant proteins remain in the retentate in the bioreactor and the permeate is substantially free of or has significantly less of either,

wherein a harvest permeate is collected using a hollow fiber filter having a pore size or molecular weight cut off that does not retain the recombinant protein in the bioreactor wherein when the harvest permeate is collected the host cells are retained in the bioreactor and the expressed recombinant proteins pass into the permeate, the fresh cell culture medium is formulated with or supplemented to achieve at least 5g/L of a non-ionic block copolymer;

wherein the null permeate is initially collected until a first predetermined parameter is reached, at which time the harvest permeate is collected for a predetermined time, the harvest permeate comprising the recombinant protein,

this is followed by alternately collecting the null permeate until a second predetermined parameter is reached, then collecting the harvest permeate for a predetermined time,

wherein the alternating collection of null permeate and harvest permeate continues until the cell culture is terminated

wherein the predetermined parameter is selected from time, viable cell density, packed cell volume, or titer.

2. The method according to claim 1, wherein the first predetermined parameter is at least 12 hours to 25 days following the establishment of the cell culture.

3. The method according to claim 1, wherein the second predetermined parameter is at least 12 to 72 hours following the collection of the harvest permeate.

4. The method according to claim 1, wherein the predetermined time is at least 12 to 72 hours.

5. The method according to claim 1, wherein the filter is a single unit filter system.

6. The method according to claim 1 further comprising taking samples during the cell culture processes, evaluating the samples to quantitatively and/or qualitatively monitor characteristics of the recombinant protein and/or the cell culture process.

7. The method according to claim 1, wherein the perfusing is continuous perfusion.

8. The method according to claim 1, wherein the perfusing is performed at a rate of less than or equal to 1.0 working volume per day.

9. The method according to claim 1, wherein the perfusing is accomplished by a peristaltic pump, a double diaphragm pump, a low shear pump or alternating tangential flow.

10. The method according to claim 1, wherein the method further comprises

subjecting the cell culture to a temperature shift wherein the cells are cultured a) at first temperature for a first period of time and b) at second temperature for a second period of time.

11. The method according to claim 10, wherein the temperature shift is in response to a predetermined parameter wherein achieving the predetermined parameter is determined using a capacitance based biomass probe.

12. The method according to claim 1 wherein the cell culture is established by inoculating the bioreactor with at least 0.1 x 10^6 viable cells/mL.

13. The method according to claim 1, wherein the mammalian cells are Chinese Hamster Ovary (CHO) cells.

14. The method according to claim 1, wherein the recombinant protein is selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a recombinant fusion protein, or a cytokine.

15. The method according to claim 1, wherein the recombinant protein is purified from the harvest permeate by one or more of flocculation, precipitation, centrifugation, depth filtration, affinity chromatography, size exclusion chromatography, ion exchange chromatography, mixed mode anion exchange chromatography, hydrophobic interaction chromatography or hydroxyapatite chromatography

16. The method according to claim 15, further comprising taking samples during the purification process, evaluating the samples to quantitatively and/or qualitatively monitor characteristics of the recombinant protein and the purification process.

17. The method according to claim 16, wherein the samples are quantitatively and/or qualitatively monitored using process analytical techniques.

18. The method according to claim 15, wherein the recombinant protein is formulated into a pharmaceutically acceptable formulation.