CLAIMS

1. A process for manufacturing a therapeutic protein substance, the process comprising:

(a) providing a liquid culture medium comprising a recombinant therapeutic protein that is substantially free of cells, wherein the liquid culture medium is fed into a periodic counter current chromatography system (PCCS);

(b) capturing the recombinant therapeutic protein in the liquid culture medium using a hydrophobic interaction or an anion exchange resin in the PCCS; and

(c) further purifying the recombinant therapeutic protein by performing hydrophobic interaction chromatography, viral inactivation, cation exchange chromatography, or affinity chromatography, to yield a therapeutic protein drug substance.

2. The process of claim 1, wherein the liquid culture medium is selected from the group consisting of: liquid culture medium removed from a perfusion bioreactor containing a culture of mammalian cells that secrete the recombinant therapeutic protein, liquid culture medium removed from a fed-batch bioreactor containing a culture of mammalian cells that secrete the recombinant therapeutic protein, and a clarified liquid culture medium from a culture of bacteria or yeast cells that secrete the recombinant protein.

3. The process of claim 2, wherein the liquid culture medium is liquid culture medium removed from a perfusion bioreactor containing a culture of mammalian cells that secrete the recombinant therapeutic protein.

4. The process of claim 3, wherein the mammalian cells are Chinese hamster ovary (CHO) cells.

5. The process of claim 1, wherein the use of the PCCS involves column switching.

6. The process of claim 1, wherein the PCCS utilizes at least two chromatography columns.

7. The process of claim 1, wherein the PCCS utilizes at least two chromatographic membranes.

8. The process of claim 1, wherein the PCCS utilizes at least one chromatography column and at least one chromatographic membrane.

9. The process of claim 1, wherein the PCCS comprises a four-column PCCS.

10. The process of claim 1, wherein step (c) includes the use of an additional PCCS.

11. The process of claim 10, wherein the use of the additional PCCS involves column switching.

12. The process of claim 10, wherein the additional PCCS utilizes at least two chromatography columns.

13. The process of claim 10, wherein the additional PCCS utilizes at least two chromatographic membranes.

14. The process of claim 10, wherein the additional PCCS utilizes at least one chromatography column and at least one chromatographic membrane.

15. The process of claim 1, wherein the liquid culture medium is held in a break tank, before being fed into the PCCS.

16. The process of claim 1, wherein the process is integrated and runs continuously from step (a) through step (c).

17. The process of claim 1, further comprising:

(d) filtering the therapeutic protein drug substance.

18. The process of claim 17, further comprising:

(e) formulating the therapeutic protein drug substance into a pharmaceutical composition.

19. The process of any one of claims 1-18, wherein the recombinant therapeutic protein is an enzyme.

20. The process of claim 19, wherein the enzyme is a recombinant galactosidase.

21. The process of claim 20, wherein the recombinant galactosidase is a recombinant α-galactosidase-A.

22. The process of claim 21, wherein the recombinant α-galactosidase-A is Fabrazyme®.

23. A process for manufacturing a therapeutic protein substance, the process comprising:

(a) culturing recombinant therapeutic protein-secreting cells in a perfusion bioreactor comprising a liquid culture medium under conditions that allow the cells to secrete the recombinant therapeutic protein into the medium, and wherein substantially cell-free volumes of the liquid culture medium are continuously or periodically removed from the perfusion bioreactor and fed into a periodic counter current chromatography system (PCCS);

(b) capturing the recombinant therapeutic protein in the liquid culture medium using a hydrophobic interaction or anion exchange resin in the PCCS; and

(c) further purifying the recombinant therapeutic protein by performing hydrophobic interaction chromatography, viral inactivation, cation exchange chromatography, or affinity chromatography, to yield a therapeutic protein drug substance.

24. The process of claim 23, wherein the mammalian cells are Chinese hamster ovary (CHO) cells.

25. The process of claim 23, wherein the use of the PCCS involves column switching.

26. The process of claim 23, wherein the PCCS utilizes at least two chromatography columns.

27. The process of claim 23, wherein the PCCS utilizes at least two chromatographic membranes.

28. The process of claim 23, wherein the PCCS utilizes at least one chromatography column and at least one chromatographic membrane.

29. The process of claim 23, wherein the PCCS comprises a four-column PCCS.

30. The process of claim 23, wherein step (c) includes the use of an additional PCCS.

31. The process of claim 23, wherein the use of the additional PCCS involves column switching.

32. The process of claim 23, wherein the additional PCCS utilizes at least two chromatography columns.

33. The process of claim 23, wherein the additional PCCS utilizes at least two chromatographic membranes.

34. process of claim 23, wherein the additional PCCS utilizes at least one chromatography column and at least one chromatographic membrane.

35. The process of claim 23, wherein the liquid culture medium is held in a break tank, before being fed into the PCCS.

36. The process of claim 23, wherein the process is integrated and runs continuously from step (a) through step (c).

37. The process of claim 23, further comprising:
(d) filtering the therapeutic protein drug substance.

38. The process of claim 37, further comprising:
(e) formulating the therapeutic protein drug substance into a pharmaceutical composition.

39. The process of any one of claims 23-38, wherein the recombinant therapeutic protein is an enzyme.

40. The process of claim 39, wherein the enzyme is a recombinant galactosidase.

41. The process of claim 40, wherein the recombinant galactosidase is a recombinant α-galactosidase-A.

42. The process of claim 41, wherein the recombinant α-galactosidase-A is Fabrazyme®.