CLAIMS

1. An integrated and continuous process for manufacturing a recombinant therapeutic protein drug 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 first multi-column chromatography system (MCCS);

(b) capturing the recombinant therapeutic protein in the liquid culture medium using the first MCCS, wherein the eluate of the first MCCS is fed into a second MCCS; and

(c) purifying and polishing the recombinant therapeutic protein using the second MCCS, thereby generating the recombinant therapeutic protein drug substance,

wherein the first MCCS is a periodic counter current chromatography system (PCCS).

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 therapeutic protein.

3. The process of claim 1 or 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 any one of claims 1-3, wherein the first MCCS only performs a single unit operation of capturing.

5. The process of any one of claims 1-3, wherein the first MCCS performs at least two different unit operations.

6. The process of claim 5, wherein the first MCCS performs the unit operations of capturing the recombinant therapeutic protein and inactivating viruses.

7. The process of any one of claims 1-6, wherein the first MCCS utilizes at least two chromatography columns.

8. The process of any one of claims 1-7, wherein the use of the first MCCS involves column switching.

9. The process of any one of claims 1-6, wherein the first MCCS utilizes at least two chromatographic membranes.

10. The process of any one of claims 1-6, wherein the first MCCS utilizes at least one chromatography column and at least one chromatographic membrane.

11. The process of any one of claims 1-10, wherein the first MCCS comprises a four-column PCCS.

12. The process of claim 11, wherein three of the four columns in the four-column PCCS perform the unit operation of capturing the recombinant therapeutic protein from the liquid.

13. The process of claim 12, wherein the capturing is performed using affinity chromatography, cation exchange chromatography, anion exchange chromatography, or molecular sieve chromatography.

14. The process of claim 13, wherein the affinity chromatography is performed with a capture mechanism selected from the group consisting of: protein A-binding capture mechanism, substrate-binding capture mechanism, antibody- or antibody fragment-binding capture mechanism, aptamer-binding capture mechanism, and cofactor-binding capture mechanism.

15. The process of any one of claims 12-14, wherein the eluate containing the recombinant therapeutic protein from the three of the four columns in the four-column PCCS is fed into the fourth column of the four-column PCCS.

16. The process of claim 15, wherein the fourth column of the four-column PCCS performs the unit operation of inactivating viruses by holding the eluate containing recombinant therapeutic protein at a low pH for viral inactivation.

17. The process of claim 16, wherein the fourth column of the four-column PCCS holds the eluate containing the recombinant therapeutic protein at a low pH for viral inactivation for a period of 10 minutes to 1.5 hours.

18. The process of any one of claims 1-17, further comprising formulating the recombinant therapeutic protein drug substance into a pharmaceutical composition.

19. The process of any one of claims 1-18, further comprising filtering the liquid culture medium before it is fed into the first MCCS.