~~WHAT IS CLAIMED IS:~~ CLAIMS

1. ~~An integrated and continuous~~ A process for manufacturing a recombinant therapeutic protein drug substance, the process comprising:

(a~~i~~) 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~~1~~);

(b~~ii~~) capturing the~~said~~ recombinant therapeutic protein in the liquid ~~culture medium~~ using the MCCS1~~, wherein the eluate of the MCCS1 containing the recombinant therapeutic protein is continuously fed into a second multi-column chromatography system (MCCS2)~~; and

(c~~iii~~) purifying and polishing the recombinant therapeutic protein, thereby generating the recombinant therapeutic protein drug substance ~~using the MCCS2, wherein the eluate from the MCCS2 is a therapeutic protein drug substance; and~~

~~wherein the process is integrated and runs continuously from said liquid culture medium to the eluate from the MCCS2 that is the 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 therapeutic protein.

3. The process of claim 1 or 2, wherein the liquid 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 MCCS only performs a single unit operation of capturing.

5.~~3.~~ The process of any one of claims 1-3~~claim 1~~, wherein the MCCS~~1 and/or the MCCS2~~ performs at least two different unit operations.

~~4. The process of claim 1, wherein the use of the MCCS1 or the MCCS2, or both, involves column switching.~~

6.~~5.~~ The process of claim 5~~3~~, wherein the MCCS~~1~~ performs the unit operations of capturing the recombinant therapeutic protein and inactivating viruses.

~~6. The process of claim 3, wherein the MCCS2 performs the unit operations of purifying and polishing the recombinant therapeutic protein.~~

7. The process of any one of claims 1-6~~claim 1~~, wherein the MCCS~~1 and/or the MCCS2~~ ultilizes at least two chromatography columns.

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

9.~~8.~~ The process of any one of claims 1-6~~claim 1~~, wherein the MCCS~~1 and/or the MCCS2~~ ultilizes at least two chromatographic membranes.

10.~~9.~~ The process of any one of claims 1-6~~claim 1~~, wherein the MCCS~~1 and/or the MCCS2~~ utilizes at least one chromatography column and at least one chromatographic membrane.

~~10. 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.~~

11. The process of any one of claims 1-10~~claim 1~~, wherein the MCCS~~1~~ is a ~~first~~ periodic counter current chromatography system (PCCS~~1~~).

12. The process of claim 11, where the PCCS~~1~~ comprises a four-column PCCS.

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

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

15. The process of claim 14, 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.

~~16. The process of claim 15, wherein the affinity chromatography is performed with a protein-A binding capture mechanism, and the recombinant therapeutic protein is an antibody or an antibody fragment.~~

16.~~17.~~ The process of any one of claims 13-15~~claim 13~~, 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.

17.~~18.~~ The process of claim 16~~17~~, 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.

18.~~19.~~ The process of claim 17~~18~~, 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 about 10 minutes to about 1.5 hours.

~~20. The process of claim 18, wherein the MCCS2 is a second periodic counter current (PCCS2) chromatography system.~~

~~21. The process of claim 20, further comprising adjusting the pH of the eluate from the fourth column of the four-column PCCS using an in-line buffer adjustment reservoir before the eluate from the fourth column of the four-column PCCS is fed into the PCCS2.~~

~~22. The process of claim 21, where the PCCS2 chromatography system comprises a three chromatography columns and a chromatographic membrane.~~

~~23. The process of claim 22, wherein the three chromatography columns in the PCCS2 perform the unit operation of purifying the recombinant therapeutic protein from the eluate of the PCCS1 through cation or anion exchange chromatography.~~

~~24. The process of claim 23, wherein the eluate from the three chromatography columns in the PCCS2 is fed into the chromatographic membrane in the PCCS2.~~

~~25. The process of claim 24, wherein the chromatographic membrane in the PCCS2 performs the unit function of polishing the recombinant therapeutic protein present in the eluate from the three chromatography columns in the PCCS2 through cation or anion exchange chromatography.~~

~~26. The process of claim 25, wherein the chromatographic membrane in the PCCS2 performs the unit function of polishing through cation exchange chromatography.~~

~~27. The process of claim 26, wherein the flow through and wash of the chromatographic membrane is the therapeutic protein drug substance.~~

19.~~28.~~ The process of any one of claims 1-18~~claim 1~~, further comprising formulating the therapeutic protein drug substance into a pharmaceutical composition.

~~29. The process of claim 1, wherein the recombinant therapeutic protein is an antibody or antibody fragment, an enzyme, an engineered protein, or an immunogenic protein or protein fragment.~~

~~30. The process of claim 23, further comprising adjusting the ionic concentration of the eluate from the three columns in the PCCS2 using in-line buffer adjustment before the eluate from the three columns in the PCCS2 is fed into the chromatographic membrane in the PCCS2.~~

~~31. The process of claim 20, further comprising the use of a break tank between the PCCS1 and the PCCS2.~~

~~32. The process of claim 20, further comprising filtering the eluate from the PCCS1 before it is fed into the PCCS2.~~

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

~~34. An integrated and continuous process for manufacturing a therapeutic protein drug substance comprising:~~

~~(i) culturing mammalian cells that secrete a recombinant therapeutic protein in a perfusion bioreactor that contains a liquid culture medium, wherein a volume of the liquid culture medium that is substantially free of cells is continuously or periodically removed from the perfusion bioreactor and fed into a first multi-column chromatography system (MCCS1);~~

~~(ii) capturing said recombinant therapeutic protein in the removed liquid culture medium using the MCCS1, wherein the eluate of the MCCS1 containing the recombinant therapeutic protein is continuously fed into a second multi-column chromatography system (MCCS2); and~~

~~(iii) purifying and polishing the therapeutic recombinant protein in the eluate of the MCCS1 using the MCCS2, wherein the eluate from the MCCS2 is a therapeutic protein drug substance;~~

~~wherein the process is integrated and runs continuously from said removed liquid culture medium to the eluate from the MCCS2 that is the therapeutic protein drug substance.~~

~~35. The process of claim 34, wherein the MCCS1 and/or the MCCS2 performs at least two different unit operations.~~

~~36. The process of claim 34, wherein the use of the MCCS1 or the MCCS2, or both, involves column switching.~~

~~37. The process of claim 35, wherein the MCCS1 performs the unit operations of capturing the recombinant therapeutic protein and inactivating viruses.~~

~~38. The process of claim 35, wherein the MCCS2 performs the unit operations of purifying and polishing the recombinant therapeutic protein.~~

~~39. The process of claim 34, wherein the MCCS1 and/or the MCCS2 ultilizes at least two chromatography columns.~~

~~40. The process of claim 34, wherein the MCCS1 and/or the MCCS2 ultilizes at least two chromatographic membranes.~~

~~41. The process of claim 34, wherein the MCCS1 and/or the MCCS2 utilizes at least one chromatography column and at least one chromatographic membrane.~~

~~42. The process of claim 34, wherein the MCCS1 is a first periodic counter current chromatography system (PCCS1).~~

~~43. The process of claim 42, where the PCCS1 comprises a four-column PCCS.~~

~~44. The process of claim 43, wherein three of the four columns in the four-column PCCS perform the unit operation of capturing the recombinant therapeutic protein from the liquid culture medium.~~

~~45. The process of claim 44, wherein the capturing is performed using affinity chromatography, cation exchange chromatography, anion exchange chromatography, or molecular sieve chromatography.~~

~~46. The process of claim 45, 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.~~

~~47. The process of claim 46, wherein the affinity chromatography is performed with a protein-A binding capture mechanism, and the recombinant therapeutic protein is an antibody or an antibody fragment.~~

~~48. The process of claim 44, 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.~~

~~49. The process of claim 48, 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.~~

~~50. The process of claim 49, 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 about 10 minutes to about 1.5 hours.~~

~~51. The process of claim 49, wherein the MCCS2 is a second periodic counter current (PCCS2) chromatography system.~~

~~52. The process of claim 51, further comprising adjusting the pH of the eluate from the fourth column of the four-column PCCS using an in-line buffer adjustment reservoir before the eluate from the fourth column of the four-column PCCS is fed into the PCCS2.~~

~~53. The process of claim 52, where the PCCS2 chromatography system comprises a three chromatography columns and a chromatographic membrane.~~

~~54. The process of claim 53, wherein the three chromatography columns in the PCCS2 perform the unit operation of purifying the recombinant therapeutic protein from the eluate of the PCCS1 through cation or anion exchange chromatography.~~

~~55. The process of claim 54, wherein the eluate from the three chromatography columns in the PCCS2 is fed into the chromatographic membrane in the PCCS2.~~

~~56. The process of claim 55, wherein the chromatographic membrane in the PCCS2 performs the unit function of polishing the recombinant therapeutic protein present in the eluate from the three chromatography columns in the PCCS2 through cation or anion exchange chromatography.~~

~~57. The process of claim 56, wherein the chromatographic membrane in the PCCS2 performs the unit function of polishing through cation exchange chromatography.~~

~~58. The process of claim 57, wherein the flow through and wash of the chromatographic membrane is the therapeutic protein drug substance.~~

~~59. The process of claim 34, further comprising formulating the therapeutic protein drug substance into a pharmaceutical composition.~~

60. The process of claim 34, wherein the recombinant therapeutic protein is an antibody or antibody fragment, an enzyme, an engineered protein, or an immunogenic protein or protein fragment.

61. The process of claim 54, further comprising adjusting the ionic concentration of the eluate from the three columns in the PCCS2 using in-line buffer adjustment before the eluate from the three columns in the PCCS2 is fed into the chromatographic membrane in the PCCS2.

62. The process of claim 51, further comprising the use of a break tank between the PCCS1 and the PCCS2.

63. The process of claim 51, further comprising filtering the eluate from the PCCS1 before it is fed into the PCCS2.

64. The process of claim 34, further comprising filtering the liquid culture medium before it is fed into the MCCS1.

65. A biological manufacturing system, comprising:

a first multi-column chromatography system (MCCS) comprising an inlet; and

a second MCCS comprising an outlet, wherein the first and second MCCSs are in fluid communication with each other, and wherein the manufacturing system is configured such that fluid is passed into the inlet, through the first and second MCCSs, and exits the manufacturing system through the outlet.

66. The system of claim 65, further comprising a bioreactor, wherein the bioreactor and the inlet are in fluid communication with each other, and wherein the manufacturing system is configured such that fluid present in the bioreactor can be passed ino the inlet.

67. The system of claim 65, wherein the first MCCS or the second MCCS, or both, is/are configured to perform at least two separate unit operations.

68. The system of claim 65, wherein the use of the MCCS1 or the MCCS2, or both, involves column switching.

~~69. The system of claim 67, wherein the first MCCS is configured to perform the unit operations of capturing the recombinant therapeutic protein and inactivating viruses.~~

~~70. The system of claim 67, wherein the second MCCS is configured to perform the unit operations of purifying and polishing the recombinant therapeutic protein.~~

~~71. The system of claim 65, wherein the first MCCS or the second MCCS, or both, contain(s) at least two chromatography columns.~~

~~72. The system of claim 65, wherein the first MCCS or the second MCCS, or both, contain(s) at least two chromatographic membranes.~~

~~73. The system of claim 65, wherein the first MCCS or the second MCCS, or both, contain(s) at least one chromatography column and at least one chromatographic membrane.~~

~~74. The system of claim 65, wherein the first MCCS is a first periodic counter current chromatography system (PCCS1).~~

~~75. The system of claim 74, wherein the PCCS1 comprises a four-column PCCS.~~

~~76. The system of claim 75, wherein three of the four columns in the four-column PCCS are capable of capturing the recombinant therapeutic protein from the liquid culture medium.~~

~~77. The system of claim 76, wherein the three of the four columns in the four-column PCCS include one or more of an affinity chromatography column, a cationic chromatography column, an anionic chromatography column, and a molecular sieve chromatography column.~~

78. The system of claim 77, wherein the three of the four columns in the four-column PCCS include one or more of an affinity chromatography column utilizing 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.

79. The system of claim 76, wherein the fourth column of the four-column PCCS is a reservoir or a column that is capable of holding eluate from the three of the four columns of the four-column PCCS containing the recombinant therapeutic protein at low pH for viral inactivation.

80. The system of claim 79, wherein the fourth column of the four-column PCCS is capable of holding the eluate containing recombinant therapeutic protein from the three of the four columns of the four-column PCCS at low pH for viral inactivation for a period of about 10 minutes to about 1.5 hours.

81. The system of claim 79, wherein the second MCCS is a second periodic counter current chromatography system (PCCS2).

82. The system of claim 65, further comprising a fluid conduit disposed between the first MCCS and the second MCCS.

83. The system of claim 82, further comprising an in-line buffer adjustment reservoir in fluid communication with the fluid conduit disposed between the first MCCS and the second MCCS, and configured such that buffer contained within the in-line buffer adjustment reservoir is introduced into the fluid present in the fluid conduit disposed between the first MCCS and the second MCCS.

84. The system of claim 82, further comprising a filter disposed in the fluid conduit between the first MCCS and the second MCCS, and configured such that the filter is capable of removing particulate matter from the fluid present in the fluid conduit between the first MCCS and the second MCCS.

~~85. The system of claim 81, wherein the PCCS2 comprises three chromatography columns and a chromatographic membrane.~~

~~86. The system of claim 85, further comprising a fluid conduit disposed between the three chromatography columns in the PCCS2 and the chromatographic membrane in the PCCS2.~~

~~87. The system of claim 86, further comprising an in-line buffer adjustment reservoir in fluid communication with the fluid conduit disposed between the three chromatography columns in the PCCS2 and the chromatographic membrane in the PCCS2, and configured such that buffer contained within the in-line buffer adjustment reservoir is introduced into the fluid present in the fluid conduit disposed between the three chromatography columns in the PCCS2 and the chromatographic membrane in the PCCS2.~~

~~88. The system of claim 85, wherein the three chromatography columns in the PCCS2 are capable of purifying the recombinant therapeutic protein through a cation or anion exchange chromatography.~~

~~89. The system of claim 85, wherein the chromatographic membrane in the PCCS2 is an cation exchange chromatographic membrane.~~

~~90. The system of claim 85, further comprising a fluid conduit between the chromatographic membrane in the PCCS2 and the outlet.~~

~~91. The system of claim 90, further comprising a filter disposed in the fluid conduit between the chromatographic membrane in the PCCS2 and the outlet, and configured such that the filter is capable of removing particulate matter from the fluid present in the fluid conduit between the chromatographic membrane in the PCCS2 and the outlet.~~

92. The system of claim 65, further comprising a pump system that is in fluid communication with the inlet.

93. The system of claim 92, wherein the pump system comprises a pump that is capable of pushing the fluid into the inlet.

94. The system of claim 92, further comprising a fluid conduit disposed between the pump and the inlet.

95. The system of claim 94, further comprising a filter disposed in the fluid conduit between the pump and the inlet, and configured such that the filter is capable of removing particulate matter from the fluid present in the fluid conduit between the pump and the inlet.

96. The system of claim 94, further comprising a break tank disposed in the fluid conduit between the pump and the inlet that is configured such that the break tank is in fluid communication with the fluid conduit between the pump and the inlet, and is capable of storing any fluid present in the fluid conduit that is not able to enter the inlet.

97. The system of claim 65, wherein the first MCCS and the second MCCS are disposed on a skid.

98. The system of claim 97, wherein the skid comprises one or more structures that enable movement.

99. The system of claim 65, wherein the first MCCS is disposed on a first skid.

100. The system of claim 99, wherein the second MCCS is disposed on a second skid.

101. The system of claim 100, wherein the first and second skids each comprise one or more structures that enable movement.

~~102. The system of claim 65, wherein the entire system is disposed on a skid.~~

~~103. The system of claim 102, wherein the skid comprises one or more structures that enable movement.~~

~~104. The system of claim 66, wherein the entire system is disposed on a skid.~~

~~105. The system of claim 104, wherein the skid comprises one or more structures that enable movement.~~

~~106. The system of claim 65, wherein the system does not include a break tank.~~

~~107. A biological manufacturing system, comprising two or more subsystems, wherein the two or more subsystems each comprise:~~

~~(i) a first multi-column chromatography system (MCCS) comprising an inlet; and~~

~~(ii) a second MCCS comprising an outlet, wherein the first and second MCCSs are in fluid communication with each other, and wherein the manufacturing system is configured such that fluid can be passed into the inlet, through the first and second MCCS, and exit the manufacturing system through the outlet;~~

~~wherein the two or more subsystems are configured such that they are each in fluid communication with a single reservoir containing a fluid, and the fluid from the single reservoir passes into the inlet of the two or more subsystems.~~

~~108. The system of claim 107, wherein each of the two or more subsystems is each disposed on its own skid.~~

~~109. The system of claim 108, wherein the skid comprises one or more structures that enable movement.~~

~~110. The system of claim 107, wherein the entire system is disposed on a skid.~~

~~111. The system of claim 110, wherein the skid comprises one or more structures that enable movement.~~