CLAIMS

What is claimed:

1. A method for detecting a column malfunction in a chromatography process, comprising:

(a) contacting a reference sample comprising a plurality of analytes and a biologic composition with a chromatography column comprising a separation composition comprising a matrix, under conditions sufficient for the biologic composition to reversibly bind to and be eluted from the matrix upon contacting the matrix with an elution composition, whereby generating a reference chromatogram from the chromatography column by plotting an absorbance value of at least a first waste composition, a second waste composition and an eluted analyte composition as a function of volume of liquid that traverses the chromatography column, wherein the plotting occurs continuously as the compositions exit the chromatography column;

(b) contacting a process sample comprising the plurality of analytes and the biologic composition with a chromatography column comprising a separation composition comprising a matrix, under conditions sufficient for the biologic composition to reversibly bind to and be eluted from the matrix upon contacting the matrix with the elution composition, whereby generating a process chromatogram from the chromatography column by plotting an absorbance value of at least a first waste composition as a function of volume of liquid that traverses the chromatography column, wherein the plotting occurs continuously as the composition exits the chromatography column;

(c) comparing the process chromatogram to the reference chromatogram thereby detecting an atypical profile in the process chromatogram, wherein the atypical profile comprises one or more features which indicate the column malfunction selected from the group consisting of:

an additional peak on the process chromatogram when compared to a comparable position on the reference chromatogram, and

a measured absorbance intensity exceeding a maximum absorbance intensity during an integral volume window,

wherein the one or more features, which indicate the column malfunction, occur prior to a step of contacting the chromatography column with an elution composition;

(d) generating a warning signal when the atypical profile is detected; and

(e) halting the chromatography process when the atypical profile is detected and until the column malfunction is resolved.

2. The method of claim 1, wherein the chromatography process comprises in ion exchange chromatography.

3. The method of claim 1, wherein the chromatography process comprises affinity chromatography.

4. The method of claim 1, wherein the chromatography process comprises hydrophobic interaction chromatography.

5. The method of any one of claims 1-4, wherein the column malfunction is caused by column deterioration.

6. The method of claim 5, wherein the column deterioration comprises column bed fracturing.

7. The method of any one of claims 1 to 6, wherein the additional peak occurs during a washing step in the chromatography process.

8. The method of any one of claims 1 to 7, wherein the magnitude of the additional peak indicates a degree of severity of the column malfunction.

9. The method of claim 8, wherein an increase in the magnitude of the additional peak indicates an increase in the degree of severity of the column malfunction of the chromatography process.

10. The method of any one of claims 1 to 9, wherein the column malfunction induces a loss of separation power of the chromatography column.

11. The method of any one of claims 1 to 10, wherein the measured absorbance intensity is determined at a wavelength corresponding to ultraviolet (UV) light.

12. The method of claim 11, wherein the measured absorbance intensity is determined at a wavelength of between 260 nanometers (nm) and 280 nm, inclusive of the endpoints.

13. The method of claim 11, wherein the measured absorbance intensity is determined at a wavelength of 260 nm, providing an A_{260} value.

14. The method of claim 11, wherein the measured absorbance intensity is determined at a wavelength of 280 nm, providing an A_{280} value.

15. The method of claim 13 or 14, wherein the maximum absorbance intensity has an A_{260} value or an A_{280} value of at least 0.05.

16. The method of any one of claims 1 to 15, wherein the reference chromatogram comprises a measured absorbance intensity that does not exceed a maximum absorbance intensity during an integral volume window and wherein the maximum absorbance intensity has an A_{260} value or an A_{280} value of 0.05 or less.

17. The method of any one of claims 1 to 16, wherein the integral volume window occurs between 1000 L and 2500 L, inclusive of the endpoints.

18. The method of claim 17, wherein the integral volume window occurs between 1250 L and 2250 L, inclusive of the endpoints.

19. The method of claim 17, wherein the integral volume window occurs between 1600 L and 1800 L, inclusive of the endpoints.

20. The method of any one of claims 1 to 19, wherein the chromatography column comprises an anion exchange resin.

21. The method of any one of claims 1 to 20, wherein the step of (a) generating the reference chromatogram comprises:

(1) binding the biologic composition to the matrix, to produce a biologic composition column and a first waste composition;

(2) contacting the biologic composition bound column of (1) and a washing composition, wherein the biologic composition remains bound to the matrix to produce a biologic composition bound column and a second waste composition;

(3) contacting the purified biologic composition column of (2) and an elution composition, wherein the biologic composition is released from the matrix into the elution composition to produce an eluted biologic composition;

(4) collecting the eluted biologic composition;

(5) simultaneously with each of steps (1)-(4), contacting each of the first waste composition, the second waste composition, and the eluted biologic composition with ultraviolet (UV) light,

(6) measuring an absorbance of the UV light of each of the first waste composition, the second waste composition, and the eluted biologic composition to produce an absorbance value for each of the first waste composition, the second waste composition, and the eluted biologic composition; and

(7) generating a chromatogram by plotting the absorbance value of each of the first waste composition, the second waste composition, and the eluted biologic composition as a function of volume of liquid that traverses the chromatography column.

22. The method of claim 21, wherein the contacting step (5) and measuring step (6) are continuous.

23. The method of claim 21 or claim 22, wherein the matrix comprises a resin.

24. The method of any one of claims 21 to 23, wherein the biologic composition is a therapeutic composition for use in a method of treatment of a human subject.

25. The method of any one of claims 1-24, wherein the warning signal is communicated electronically to a processor and wherein the processor is operably linked to the chromatography column.

26. The method of claim 25, wherein the processor receives the warning signal and interrupts the chromatography process or prevents the initiation of a further chromatography process until the column malfunction is resolved.

27. The method of any one of claims 1 to 26, wherein resolving the column malfunction comprises repacking the chromatography column.

28. The method of any one of claims 1 to 27, wherein the biologic composition comprises a therapeutic protein.

29. The method of claim 28, wherein the therapeutic protein in the reference sample is the same or substantially similar to the therapeutic protein in the process sample.

30. The method of any one of claims 1 to 29, wherein the biologic composition comprises a VEGF-Trap protein.

31. The method of claim 1, wherein the step of (b) generating the process chromatogram comprises:

(1) binding the biologic composition to the matrix, to produce a biologic composition bound column and a first waste composition;

(2) contacting the biologic composition bound column of (1) and a washing composition, wherein the biologic composition remains bound to the matrix to produce a purified biologic composition bound column and a second waste composition;

(3) contacting the purified biologic composition bound column of (2) and an elution composition, wherein the biologic composition is released from the matrix into the elution composition to produce an eluted biologic composition;

(4) collecting the eluted biologic composition;

(5) simultaneously with each of steps (1)-(4), contacting each of the first waste composition, the second waste composition, and the eluted biologic composition with ultraviolet (UV) light,

(6) measuring an absorbance of the UV light of each of the first waste composition, the second waste composition, and the eluted biologic composition to produce an absorbance value for each of the first waste composition, the second waste composition, and the eluted biologic composition; and

(7) generating a chromatogram by plotting the absorbance value of each of the first waste composition, the second waste composition, and the eluted biologic composition as a function of volume of liquid that traverses the chromatography column

wherein generating the process chromatogram occurs simultaneously with contacting each of the first waste composition, the second waste composition, and the eluted biologic composition with ultraviolet (UV) light, and

wherein the chromatography process is interrupted prior to step (3) upon detection of an atypical profile until the column malfunction is resolved.