~~**WHATS IS CLAIMED IS:**~~

~~1.~~ **CLAIMS:**

1. A method, comprising:

obtaining a vibrational spectrum of a solution in a biological manufacturing system;

analyzing the vibrational spectrum using a first chemometrics model to determine a value of a first quality attribute associated with the solution;

analyzing the vibrational spectrum using a second chemometrics model to determine a value of a second quality attribute associated with the solution; and

adjusting at least one parameter of a purification unit of the biological manufacturing system based on at least one of the values of the first and second quality attributes~~.~~.

~~2.~~ wherein at least one of the first and second quality attributes is selected from the group consisting of protein aggregation, charge variant distribution, glycan profile, product integrity, protein fragments, nucleic acid fragments, empty capsids, host cell protein quantity, residual host DNA, residual helper virus, residual helper viral proteins, residual helper viral DNA, and residual column ligands.

2. The method of claim 1, further comprising using the biological manufacturing system to produce at least one of a protein-based therapeutic substance, a nucleic acid-based drug substance, and a gene therapy drug substance.

3. ~~3.~~ The method of claim 1, wherein at least one of the first and second quality attributes ~~are each independently~~is selected from the group consisting of product quality attributes, product-related impurities, and process-related impurities, for a biological product produced by the biological manufacturing system.

4. ~~4.~~ The method of claim 1, wherein obtaining the vibrational spectrum comprises directing radiation to be incident on the solution and measuring attenuated totally reflected radiation from the solution.

5. ~~5.~~ The method of claim 4, wherein the radiation is incident on the solution by passing through a radiation window, and wherein the attenuated totally reflected radiation passes through the radiation window before it is measured, the method further comprising measuring the attenuated totally reflected radiation from the solution while the solution is flowing relative to the radiation window.

6. ~~6.~~ The method of claim 1, wherein the first chemometrics model comprises a first set of principal vibrational components correlated with the first quality attribute.

7. ~~7.~~ The method of claim 6, wherein the first chemometrics model comprises at least three principal vibrational components.

8. ~~8.~~ The method of claim 6, wherein analyzing the vibrational spectrum using the first chemometrics model comprises calculating the first quality attribute value based on the first set of principal vibrational components.

9. ~~9.~~ The method of claim 6, wherein the second chemometrics model comprises a second set of principal vibrational components correlated with the first quality attribute.

10. ~~10.~~ The method of claim 9, wherein the first and second sets of principal vibrational components have no members in common.

11. ~~11.~~ The method of claim 9, wherein analyzing the vibrational spectrum using the second chemometrics model comprises calculating the second quality attribute value based on the second set of principal vibrational components.

12. ~~12.~~ The method of claim 1, wherein the solution comprises a solution discharged from a purification unit of the biological manufacturing system.

13. ~~13.~~ The method of claim 1, further comprising obtaining the vibrational spectrum by measuring radiation from the solution as the solution flows between a first purification unit and a second purification unit of the biological manufacturing system.

14. ~~14.~~ The method of claim 1, further comprising obtaining the vibrational spectrum by measuring radiation from the solution after the solution flows out of a final purification unit of the biological manufacturing system.

15. ~~15.~~ The method of claim 1, wherein the solution is a first solution, the method further comprising:

obtaining a vibrational spectrum of a second solution in the biological manufacturing system;

analyzing the vibrational spectrum of the second solution using the first chemometrics model to determine a value of the first quality attribute for the second solution; and

analyzing the vibrational spectrum of the second solution using the second chemometrics model to determine a value of the second quality attribute for the second solution.

16. ~~16.~~ The method of claim 15, wherein the first solution flows between a first purification unit and a second purification unit of the biological manufacturing system, and the second solution flows between the second purification unit and a third purification unit of the biological manufacturing system.

17. ~~17.~~ The method of claim 15, further comprising adjusting the at least one parameter based on at least one of the first and second quality attribute values for the first solution, and the first and second quality attribute values for the second solution.

18. ~~18.~~ The method of claim 4, further comprising obtaining the vibrational spectrum and determining the first and second quality attribute values within a time period of 30 seconds or less, starting from a time at which the radiation is incident on the solution.

19. ~~19.~~ The method of claim 1, further comprising:

repeating the steps of obtaining the vibrational spectrum, analyzing the vibrational spectrum using the first chemometrics model, and analyzing the vibrational spectrum using the second chemometrics model, to determine a temporal sequence of first quality attribute values and second quality attribute values associated with successive portions of the solution; and

adjusting the at least one parameter based on at least one of the temporal sequence of first quality attribute values and the temporal sequence of second quality attribute values.

20. ~~20.~~ The method of claim 9, further comprising:

obtaining a set of one or more calibration spectra representative of the solution; and

analyzing the set of calibration spectra to determine the first and second sets of principal vibrational components.

21. ~~21.~~ The method of claim 20, wherein the first chemometrics model comprises a first set of coefficients associated with the first set of principal vibrational components and the second chemometrics model comprises a second set of coefficients associated with the second set of principal vibrational components, the method further comprising determining the first and second sets of coefficients based on a regression analysis.

22. ~~22.~~ The method of claim 1, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting of concentration, ~~aggregates, charge variant distribution,~~ purity, ~~glycan profile,~~and identity~~, and integrity~~.

23. ~~23.~~ The method of claim 1, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting of ~~protein fragments, nucleic acid fragments,~~ nucleic acid variants~~, empty capsids, and~~ vector impurities.

24. ~~24.~~ The method of claim 1, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting ~~of host cell proteins, residual host DNA, residual column ligands,~~ impurity concentration~~,~~ and impurity amount~~, residual helper virus, residual helper viral proteins, and residual helper viral DNA~~.

25. ~~25.~~ A biological manufacturing system, comprising:

a bioreactor configured to produce a solution comprising a biological product;

a purification unit configured to receive the solution;

a radiation source configured to direct radiation to be incident on the solution;

a detection apparatus configured to measured radiation from the solution; and

a system controller connected to the bioreactor and the detection apparatus, and configured to:

receive a measurement signal from the detection apparatus corresponding to information about a vibrational spectrum of the solution;

analyze the information using a first chemometrics model to determine value of a first quality attribute associated with the solution;

analyze the information using a second chemometrics model to determine a value of a second quality attributed associated with the solution; and

adjust at least one parameter of the purification unit based on at least one of the values of the first and second quality attributes~~.~~,

~~26.~~ wherein at least one of the first and second quality attributes is selected from the group consisting of protein aggregation, charge variant distribution, glycan profile, product integrity, protein fragments, nucleic acid fragments, empty capsids, host cell protein quantity, residual host DNA, residual helper virus, residual helper viral proteins, residual helper viral DNA, and residual column ligands.

26. The system of claim 25, further comprising a flow cell positioned so that the solution passes through the flow cell, and the radiation source directs the radiation to be incident on the solution while the solution is in the flow cell.

27. ~~27.~~ The system of claim 25, wherein the biological product comprises at least one of a protein-based therapeutic substance, a nucleic acid-based drug substance, and a gene therapy drug substance.

28. ~~28.~~ The system of claim 27, wherein the protein-based therapeutic substance comprises at least one of a protein, a peptide, an antibody, and an enzyme.

29. ~~29.~~ The system of claim 27, wherein the nucleic acid-based drug substance comprises at least one of DNA, a plasmid, an oligonucleotide, an aptamer, a DNAzyme, an RNA aptamer, an RNA decoy, a microRNA fragment, and a small interfering RNA fragment.

30. ~~30.~~ The system of claim 25, wherein at least one of the first and second quality attributes ~~are each independently~~is selected from the group consisting of product quality attributes, product-related impurities, and process-related impurities, for a biological product produced by the biological manufacturing system.

31. ~~31.~~ The system of claim 26, wherein the detector comprises a total internal reflection sensor configured to measure attenuated totally reflected radiation from the solution.

32. ~~32.~~ The system of claim 31, wherein the total internal reflection sensor is integrated with a portion of the flow cell.

33. ~~33.~~ The system of claim 31, wherein the controller and detection apparatus are configured to measure the attenuated totally reflected radiation from the solution while the solution is flowing within the flow cell.

34. ~~34.~~ The system of claim 25, wherein the first chemometrics model comprises a first set of principal vibrational components correlated with the first quality attribute.

35. ~~35.~~ The system of claim 34, wherein the controller is configured to analyze the vibrational spectrum using the first chemometrics model by calculating the first quality attribute value based on the first set of principal vibrational components.

36. ~~36.~~ The system of claim 34, wherein the second chemometrics model comprises a second set of principal vibrational components correlated with the first quality attribute.

37. ~~37.~~ The system of claim 36, wherein the first and second sets of principal vibrational components have no members in common.

38. ~~38.~~ The system of claim 36, wherein the controller is configured to analyze the vibrational spectrum using the second chemometrics model by calculating the second quality attribute value based on the second set of principal vibrational components.

39. ~~39.~~ The system of claim 25, wherein the solution comprises a solution discharged from the purification unit.

40. ~~40.~~ The system of claim 39, wherein the controller is connected to the purification unit and configured to purify the solution in the purification unit prior to obtaining the information about the vibrational spectrum of the solution.

41. ~~41.~~ The system of claim 25, wherein the purification unit is a first purification unit of the system, and the system further comprises:

a second purification unit configured to receive the solution,

wherein the detection apparatus is positioned to measure radiation from the solution as the solution flows between the first purification unit and the second purification unit.

42. ~~42.~~ The system of claim 25, wherein the solution is a first solution, and the detection apparatus is further configured to measure radiation from a second solution, and the controller is configured to:

receive a measurement signal from the detection apparatus corresponding to information about a vibrational spectrum of the second solution;

analyze the information about the second solution using the first chemometrics model to determine a value of the first quality attribute for the second solution; and

analyze the information about the second solution using the second chemometrics model to determine a value of the second quality attribute for the second solution.

43. ~~43.~~ The system of claim 42, wherein the purification unit is a first purification unit and the system comprises a second purification unit and a third purification unit, and wherein:

the first solution flows between the first purification unit and the second purification unit; and

the second solution flows between the second purification unit and the third purification unit.

44. ~~44.~~ The system of claim 42, wherein the controller is configured to adjust the at least one parameter based on at least one of the first and second quality attribute values for the first solution, and the first and second quality attribute values for the second solution.

45. ~~45.~~ The system of claim 31, wherein the detection apparatus and controller are configured to measure the radiation from the solution and determine the first and second quality attribute values within a time period of 30 seconds or less, starting from a time at which the radiation is incident on the solution.

46. ~~46.~~ The system of claim 25, wherein the detection apparatus and controller are configured to repeat the steps of measuring the radiation from the solution, analyzing the information about the vibrational spectrum of the solution using the first chemometrics model, and analyzing the vibrational spectrum using the second chemometrics model, to determine a temporal sequence of first quality attribute values and second quality attribute values associated with successive portions of the solution.

47. ~~47.~~ The system of claim 46, wherein the controller is further configured to adjust the at least one parameter based on at least one of the temporal sequence of first quality attribute values and the temporal sequence of second quality attribute values.

48. ~~48.~~ The system of claim 36, wherein the controller is configured to obtain a set of one or more calibration spectra representative of the solution, and to analyze the set of calibration spectra to determine the first and second sets of principal vibrational components.

49. ~~49.~~ The system of claim 25, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting of concentration, ~~aggregates, charge variant distribution,~~ purity, ~~glycan profile,~~and identity~~, and integrity~~.

50. ~~50.~~ The system of claim 25, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting of ~~protein fragments, nucleic acid fragments,~~ nucleic acid variants~~, empty capsids,~~ and vector impurities.

51. ~~51.~~ The system of claim 25, wherein ~~at least~~ one of the first and second quality attributes is selected from the group consisting of ~~host cell proteins, residual host DNA, residual column ligands,~~ impurity concentration~~,~~ and impurity amount~~, residual helper virus, residual helper viral proteins, and residual helper viral DNA~~.