We claim:

1. A method of producing a concentrated protein purification intermediate comprising:

providing a universal model produced using a plurality of protein purification intermediates;

determining concentrations of a protein purification intermediate in-real time using *in situ* Raman spectroscopy with the universal model while concentrating the protein purification intermediate; and

adjusting parameters of the concentrating step in-real time to obtain the concentrated protein purification intermediate and/or final concentrated pool, and

wherein the concentration of the protein purification intermediate is at least 150 mg/mL.

2. The method of claim 1, wherein the concentrated protein product has a concentration of 1505 mg/mL to 300 mg/mL.

~~3. The method of any one of claims 1 or 2, wherein the concentration of the protein purification intermediate is at least 50 mg/mL.~~

~~4. The method of any one of claims 1 or 2, wherein the concentration of the protein purification intermediate is at least 150 mg/mL.~~

3.~~5.~~ The method of claim 1~~any one of claims 1-4~~, wherein the protein purification intermediate is concentrated using ultrafiltration, buffer exchange, or both.

4.~~6.~~ The method of claim 1~~any one of claims 1-5~~, wherein the protein purification intermediate is harvested from a bioreactor, a fed-batch culture, or a continuous culture.

5.~~7.~~ The method of ~~any one of claims~~ claim 1~~-6~~, wherein determining the concentration of the protein purification intermediate occurs continuously or intermittently in real-time.

6.~~8.~~ The method of ~~any one of~~ claim~~s~~ 1~~-6~~, wherein the quantifying of protein concentration is performed in intervals from 30 seconds to 10 minutes, hourly, or daily.

79. The method of ~~any one of~~ claim~~s~~ 1~~-8~~, wherein the protein purification intermediate is an antibody or antigen binding fragment thereof, a fusion protein, or a recombinant protein.

~~10. The method of any one of claims 1-9, wherein spectral data is collected at one or more wavenumber ranges selected from the group consisting of 977-1027 cm^{-1}, 1408-1485 cm^{-1}, 1621-1711 cm^{-1}, 2823-3046 cm^{-1}, and combinations thereof.~~

811. A method of producing a protein purification intermediate comprising:

independently performing Raman Spectroscopy analysis on a plurality of protein purification intermediates to produce a universal model capable of quantifying any one of the plurality of protein purification intermediates;

determining concentrations of a protein purification intermediate using *in situ* Raman spectroscopy with the universal model during concentration of the protein purification intermediate; and

producing the concentrated protein purification intermediate when the concentrated protein purification intermediate reaches a predetermined concentration or the final concentrated pool target, and

wherein the concentration of the protein purification intermediate is at least 150 mg/mL.

912. The method of claim 811, wherein the model is produced using Partial Least Squares Regression Analysis of raw spectral data and offline protein concentration data.

1013. The method of claim 912, further comprising performing a normalization technique or point-smoothing on the Raman spectroscopy data.

1114. The method of claim 1013, wherein the normalization technique comprises standard normal variate.

1215. The method of claim 1013, wherein the point-smoothing comprises 1st derivative with 21 cm^{-1} smoothing.

13~~16~~. The method of claim 8~~any one of claims 11-15~~, wherein the model provides predicted protein concentration values for a plurality of protein purification intermediates with ≤5% error compared to off-line protein concentration values.

14~~17~~. The method of claim 8~~any one of claims 11-15~~, wherein the model provides predicted protein concentration values for a plurality of protein purification intermediates with ≤3% error compared to off-line protein concentration values.

15~~18~~. The method of claim 8~~11~~, wherein the concentrated protein purification intermediate has a concentration of 150~~5~~ mg/mL to 300 mg/mL.

~~19. The method claim 11, wherein the concentration of the concentrated protein purification intermediate is at least 100 mg/mL.~~

~~20. The method of claim 11, wherein the concentration of concentrated protein purification intermediate is at least 150 mg/mL.~~

16~~21~~. The method of claim 8~~11~~, wherein the concentrated protein purification intermediate is concentrated using ultrafiltration, diafiltration, or both.

17~~22~~. The method of claim 8~~11~~, wherein the concentrated protein purification intermediate is harvested from a bioreactor, a fed-batch culture, or a continuous culture.

18~~23~~. The method of ~~any one of claims~~ claim 1~~-22~~, wherein determining the concentration of the protein purification intermediate occurs continuously or intermittently in real-time.

19~~24~~. The method of ~~any one of~~ claim~~s~~ 1~~-23~~, wherein the quantifying of protein concentration is performed in intervals from 30 seconds to 10 minutes, hourly, or daily.

20~~25~~. The method of ~~any one of~~ claim~~s~~ 8 ~~11 24~~, wherein the protein purification intermediate is an antibody or antigen binding fragment thereof, a fusion protein, or a recombinant protein.

21~~26~~. The protein purification intermediate produced according to ~~any one of~~ claim~~s~~ 1 ~~25~~.

22~~27~~. A method of monitoring and controlling critical quality attributes in a protein purification intermediate during downstream protein purification processing comprising:

providing a universal model produced using a plurality of protein purification intermediates;

quantifying one or more critical quality attributes in the protein purification intermediate using *in situ* Raman spectroscopy; and

adjusting the one or more critical quality attributes in the protein purification intermediate to match predetermined critical quality attribute levels, and

wherein the concentration of the protein purification intermediate is at least 150 mg/mL.

23~~28~~. The method of claim 22~~27~~, wherein the critical quality attributes is selected from the group consisting of antibody titer, protein concentration, high molecular weight species, drug-antibody ratio and buffer excipients.

24~~29~~. The method of ~~any one of claims 27 or 28~~claim 22, wherein the downstream protein purification processing is ultrafiltration/diafiltration.

25~~30~~. A method for monitoring and controlling the levels of excipients in harvested cell culture fluid and/or protein purification intermediate during downstream purification comprising:

providing a universal model produced using a plurality of protein purification intermediates;

determining concentrations of the excipients in-real time using *in situ* Raman spectroscopy while purifying the cell culture fluid or protein purification intermediate; and

adjusting parameters of the purification step in-real time to obtain or maintain predetermined amounts of the excipients in the harvested cell culture fluid and/or protein purification intermediate, and

wherein the concentration of the protein purification intermediate is at least 150 mg/mL.

2631. The method of claim 2530, wherein the excipient comprises a buffer excipient.

2732. The method of ~~any one of claims 30 or 31~~claim 25, wherein the excipient is selected from the group consisting of acetate, citrate, histidine, succinate, phosphate, hydroxymethylaminomethane (Tris), proline, arginine, sucrose, or combinations thereof.

2833. The method of claim 2530, wherein the excipient comprises a surfactant excipient.

2934. The method of ~~any one of claims 30 or 33~~claim 28, wherein the surfactant excipient is selected from the group consisting of polysorbate 80, polysorbate 20, and poloxamer 188.

3035. The method of claim 811, further comprising an excipient, wherein the excipient comprises polyethylene glycol and/or sucrose.

31. The method of claim 1, further comprising:

independently performing Raman Spectroscopy analysis on a plurality of protein purification intermediates to produce the universal model, wherein the universal model is capable of quantifying any one of the plurality of protein purification intermediates during primary concentration and/or diafiltration at a concentration between 0-120 g/L, and/or during final concentration at a concentration greater than 200 g/L in an ultrafiltration/diafiltration (UF/DF) system.

32. The method of claim 1, further comprising:

determining concentrations of an excipient in-real time using in situ Raman spectroscopy while purifying the harvested cell culture fluid and/or protein purification intermediate; and

adjusting parameters of the purification step in-real time to obtain or maintain predetermined amounts of the excipients in the harvested cell culture fluid and/or protein purification intermediate.

33. The method of claim 1, further comprising:

quantifying one or more critical quality attributes in the protein purification intermediate using in situ Raman spectroscopy; and

adjusting the one or more critical quality attributes in the protein purification intermediate to match predetermined critical quality attribute levels,

wherein the critical quality attributes is selected from the group consisting of antibody titer, protein concentration, high molecular weight species, drug-antibody ratio and buffer excipients.

34. The method of claim 1, wherein spectral data is collected at one or more wavenumber ranges selected from the group consisting of 977-1027 cm^{-1}, 1408-1485 cm^{-1}, 1621-1711 cm^{-1}, 2823-3046 cm^{-1}, and combinations thereof.

35. The method of claim 1, wherein the protein purification intermediate is a fusion protein.

36. The method of claim 1, wherein the protein purification intermediate comprises an extracellular domain of a cell surface receptor or a fragment thereof.

37. The method of claim 1, wherein the protein purification intermediate is a recombinant protein.

38. The method of claim 1, wherein the protein purification intermediate is a recombinant fusion protein.

39. The method of claim 1, wherein the protein purification intermediate comprises an Fc-fusion protein or fragment thereof.

40. The method of claim 1, wherein the protein purification intermediate comprises an anti-VEGF antibody or fragment thereof.

41. The method of claim 1, wherein the protein purification intermediate is an antibody or antigen binding fragment thereof.