

WHAT IS CLAIMED IS:

1. A continuous method for producing an antibody drug conjugate (ADC) composition comprising (i) conjugating an antibody or antigen-binding fragment thereof to a drug to form an ADC in a flow reactor, (ii) removing unconjugated drug, and (iii) exchanging the ADC into a stable buffer, wherein (i) to (iii) are performed continuously, and wherein single-pass tangential flow filtration (SPTFF), flow-through column-chromatography, and/or countercurrent diafiltration is used to remove the unconjugated drug.
2. The method of claim 1, wherein SPTFF ~~and/or countercurrent diafiltration~~ is used to remove the unconjugated drug and to exchange the ADC into the stable buffer.
3. The method of claim 1, wherein flow-through column chromatography is used to remove the unconjugated drug, ~~and SPTFF and/or countercurrent diafiltration is used to exchange the ADC into the stable buffer.~~
- 3.4. The method of claim 1, wherein countercurrent diafiltration is used to remove the unconjugated drug.
- 4.5. The method of any one of claims 1-34, further comprising pre-processing the antibody or antigen-binding fragment thereof.
5. The method of claim 4, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed continuously with (i) to (iii).
6. The method of claim 4 or 5, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed using SPTFF and/or countercurrent diafiltration, optionally wherein only one SPTFF or countercurrent diafiltration step is used in the pre-processing.
7. The method of claim 45, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed in bulk prior to (i) to (iii).
8. The method of any one of claims 1-7, wherein the method further comprises pre-processing the drug for conjugation.

9. A continuous method for producing an antibody drug conjugate (ADC) composition comprising (i) pre-processing an antibody or antigen-binding fragment thereof, (ii) conjugating the antibody or antigen-binding fragment thereof to a drug to form an ADC in a flow reactor, (iii) removing unconjugated drug, and (iv) exchanging the ADC into a stable buffer, wherein (i) to (iv) are performed continuously, and wherein single-pass tangential flow filtration (SPTFF), flow-through column-chromatography, and/or countercurrent diafiltration is used to remove the unconjugated drug.
10. The method of any one of claims 4-9, wherein the pre-processing of the antibody or antigen-binding fragment thereof comprises exchanging the antibody or antigen-binding fragment thereof into a buffer for conjugation.
11. The method of any one of claims 4-10, wherein the pre-processing of the antibody or antigen-binding fragment thereof comprises reducing the antibody or antigen-binding fragment thereof and/or oxidizing the antibody or antigen-binding fragment thereof, optionally wherein (a) the reducing and/or the oxidizing are achieved without using SPTFF or countercurrent diafiltration or (b) the reducing and/or the oxidizing are achieved using only one SPTFF or countercurrent diafiltration step.
12. A method for producing an antibody drug conjugate (ADC) in a continuous conjugation process, comprising (i) adding one or more conjugation reaction reagents to a conjugation reaction in a flow reactor while the conjugation reaction proceeds and after at least one ADC has formed and (ii) continuously removing unconjugated drug using (SPTFF), flow-through column-chromatography, and/or countercurrent diafiltration.
13. The method of claim 12, wherein the conjugation reaction reagent comprises an antibody.
14. The method of claim 12 or 13 wherein the conjugation reaction reagent comprises a drug attached to a linker.
15. The method of claim 12 wherein the conjugation reaction reagent comprises an antibody or antigen-binding fragment thereof attached to a linker.
16. The method of any one of claims 12-15, further comprising pre-processing an antibody or antigen-binding fragment thereof.

17. The method of claim 16, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed continuously with the conjugation reaction.
18. The method of claim 16 or 17, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed using SPTFF and/or countercurrent diafiltration, optionally wherein only one SPTFF or countercurrent diafiltration step is used in the pre-processing.
19. The method of claim 16, wherein the pre-processing of the antibody or antigen-binding fragment thereof is performed in bulk prior to the conjugation reaction.
20. The method of any one of claims 16-19, wherein the pre-processing of the antibody or antigen-binding fragment thereof comprises exchanging the antibody or antigen-binding fragment thereof into a buffer for conjugation.
21. The method of any one of claims 16-20, wherein the pre-processing of the antibody or antigen-binding fragment thereof comprises reducing the antibody or antigen-binding fragment thereof and/or oxidizing the antibody or antigen-binding fragment thereof.
22. The method of any one of claims 5-10 wherein the ADC is concentrated using single-pass tangential flow filtration and/or countercurrent diafiltration.
23. The method of any one of claims 5-11 wherein the ADC is purified using single-pass tangential flow filtration and/or countercurrent diafiltration.
24. The method of any one of claims 5-12, wherein the ADC is transferred to a formulation buffer using single-pass tangential flow filtration and/or countercurrent diafiltration.
25. The method of any one of claims 12-214, wherein the ADC is concentrated, purified, and/or transferred to a formulation buffer using flow-through [column](#)-chromatography.
26. The method of claim 22, wherein the single-pass tangential flow filtration uses an ultrafiltration membrane.
27. The method of claim 23 or 24, wherein the single-pass tangential flow filtration uses a diafiltration membrane.

28. The method of any one of claims 1-27 wherein the method improves the consistency of the ADC production.
29. The method of any one of claims 1-28 wherein the ~~wherein the~~ method decreases the time for ADC production.
30. The method of any one of claims 1-11, 18, 20-24, and 26-29 wherein the single-pass tangential flow filtration and/or the ~~or~~ countercurrent diafiltration improves the consistency of the ADC production.
31. The method of any one of claims 1-11, 18, 20-24, and 26-30 wherein the single-pass tangential flow filtration and/or the ~~or~~ countercurrent diafiltration decreases the time for ADC concentration, purification, or transfer.
32. The method of any one of claims 1-11, 18, 20-24, and 26-31 wherein the single-pass tangential flow filtration and/or the ~~or~~ countercurrent diafiltration decreases the amount of buffer used.
33. The method of any one of claims 1-32, wherein the method further comprises in-line monitoring of an analyte.
34. The method of any one of claims 1-33, wherein the ADC comprises an antibody.
35. The method of any one of claims 1-33, wherein the ADC comprises an antigen-binding fragment of an antibody.
36. The method of any one of claims 1-33, wherein the ADC comprises an antibody or antigen-binding fragment that specifically binds to CD37, CD33, FOLR1, CD123, CD19, cMET, ADAM9, or HER2.
37. The method of claim 36, wherein the antibody or antigen-binding fragment thereof comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of huMov19, Z4681A, or G4732A.
38. The method of claim 37, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

39. The method of claim 36, wherein the antibody or antigen-binding fragment thereof comprises VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences comprising the sequences of SEQ ID NOs:1-6, respectively, SEQ ID NOs:7-12, respectively, SEQ ID NOs:13-18, respectively, SEQ ID NOs:19-24, respectively, SEQ ID NOs:25-30, or respectively, SEQ ID NOs:31-36, respectively.
40. The method of claim 36, wherein the antibody or antigen-binding fragment thereof comprises VH and VL sequences comprising the sequence of SEQ ID NOs:37 and 38, respectively, SEQ ID NOs:37 and 39, respectively, SEQ ID NOs:40 and 41, respectively, SEQ ID NOs:42 and 43, respectively, SEQ ID NOs:44 and 45, respectively, SEQ ID NOs: 46 and 47, respectively, or SEQ ID NOs:48 and 49, respectively.
41. The method of claim 36, wherein the antibody comprises heavy and light chain sequences comprising the sequences of SEQ ID NOs:50 and 51, respectively, SEQ ID NOs:50 and 52, respectively, SEQ ID NOs:53 and 54, respectively, or SEQ ID NOs:55 and 56, respectively.
42. The method of any one of claims 1-41, wherein the ADC comprises a linker selected from the group consisting of SMCC, sSPDB, and a peptide linker.
43. The method of any one of claims 1-42, wherein the ADC comprises a maytansinoid or an indolino-benzodiazepine.
44. The method of claim 43, wherein the maytansinoid is DM1 or DM4.
45. The method of claim 43, wherein the indolino-benzodiazepine is DGN462 or DGN549.
46. The method of any one of claims 1-45 wherein the ADC is IMGN529, IMGN779, IMGN853, or IMGN632, ~~or~~ Kadcyla.
47. A method for producing IMGN853 comprising (i) mixing huMov19 antibody and DM4-linked to sulfo-SPDB in a continuous conjugation process to form IMGN853 in a flow reactor, (ii) purifying IMGN853 using single-pass tangential flow filtration and/or countercurrent diafiltration, and (iii) exchanging the IMGN853 into a formulation buffer using single-pass tangential flow filtration and/or countercurrent diafiltration, wherein (i) to (iii) are performed continuously.

48. A method for producing IMG779 comprising (i) mixing Z4681A antibody and DGN462-linked to sulfo-SPDB in a continuous conjugation process to form IMG779 in a flow reactor, (ii) purifying IMG779 using single-pass tangential flow filtration and/or countercurrent diafiltration, and (iii) exchanging the IMG779 into a formulation buffer using single-pass tangential flow filtration and/or countercurrent diafiltration, wherein (i) to (iii) are performed continuously.
49. A method for producing IMG632 comprising (i) mixing G4732A antibody and sulfonated DNG549C in a continuous conjugation process to form IMG632 in a flow reactor, (ii) purifying IMG632 using single-pass tangential flow filtration and/or countercurrent diafiltration, and (iii) exchanging the IMG632 into a formulation buffer using single-pass tangential flow filtration and/or countercurrent diafiltration, wherein (i) to (iii) are performed continuously.
50. The method of any one of claims 1-49, wherein the method comprises increasing a first temperature of a conjugation process by at least 5°C to an elevated temperature that is no more than 55°C, wherein the elevated temperature is maintained for no more than 20 minutes.
51. The method of any one of claims 1-49, wherein the method comprises decreasing a first temperature of a conjugation process by at least 5°C and no more than 30 °C to a reduced temperature, wherein the reduced temperature is maintained for no more than 20 minutes.
52. The method of any one of claims 1-51, wherein the method comprises changing a first pH of a conjugation process by at least 0.5 to an altered pH, wherein the altered pH does not exceed 9 and does not go below 4, and wherein the altered pH is maintained for no more than 20 minutes.