Claims

1. A method of reducing potency variability in a composition comprising an antibody drug conjugate, the method comprising:
    (a) determining drug concentration at a target antibody concentration and a fixed drug antibody ratio (DAR);
    (b) targeting a variable drug concentration which identifies the midpoint of a range where an antibody concentration specification range and a drug concentration specification range overlap;
    (c) formulating the antibody drug conjugate composition to the targeted variable drug concentration, thereby reducing potency variability in the composition;
    wherein the variability in the target drug concentration is ± 10%..

2. The method of claim 1, wherein the variability is less than 5, 6, 7, 8, or 9%.

3. The method of claim 1, wherein the variability in the antibody concentration is ± 10%; optionally wherein the variability is less than 5, 6, 7, 8, or 9%.

4. A method of reducing potency variability in a composition comprising an antibody drug conjugate, the method comprising:
    (a) measuring the DAR for the antibody drug conjugate composition;
    (b) determining the upper antibody specification limit and the lower antibody specification limit, wherein the upper antibody specification limit is the target antibody concentration plus the maximum variation allowed by the specification and the lower antibody specification limit is the target antibody concentration minus the maximum variation allowed by the specification;
    (c) determining the defined upper drug specification limit and the defined lower drug specification limit, wherein the defined upper drug specification limit is the target drug concentration plus the maximum variation allowed by the specification and the defined lower drug specification limit is the target drug concentration minus the maximum variation allowed by the specification;

(d) determining the calculated upper drug specification limit (USL (drug)) as follows:

$$\text{USL (drug) } \mu g/mL = \frac{\text{Upper Antibody Concentration Specification Limit x DAR x Drug Mol. Wt.}}{\text{Antibody Mol. Wt.}} \times 1000$$

(e) determining the calculated lower drug specification limit (LSL (drug)) as follows:

$$\text{LSL (drug) } \mu g/mL = \frac{\text{Lower Antibody Concentration Specification Limit x DAR x Drug Mol. Wt.}}{\text{Antibody Mol. Wt.}} \times 1000$$

(f) comparing the calculated USL (drug) of step (d) to the defined upper drug specification limit of step (c), and selecting the lower of the two values as the effective upper drug specification limit;

(g) comparing the calculated LSL (drug) of step (e) to the defined lower drug specification limit of step (c), and selecting the higher of the two values as the effective lower drug specification limit; and

(h) formulating the antibody drug conjugate composition to a target drug concentration that is the midpoint between the effective upper drug specification limit and the effective lower drug specification limit, thereby reducing potency variability in said composition.

5. The method of claim 4, wherein the method narrows the range of the upper and lower specification limits for the drug and the antibody to ± 3-9%;

optionally wherein the method narrows the range of the upper and lower specification limits for the drug to ± 4%.

6. The method of claim 4, wherein the maximum variation allowed by the specification in step (b) is ± 15%;

optionally wherein the maximum variation allowed by the specification in step (b) is less than 10, 11, 12, 13, or 14%.

7. The method of claim 4, wherein the maximum variation allowed by the specification in step (c) is ± 15%;

optionally wherein the maximum variation allowed by the specification in step (c) is less than 10, 11, 12, 13, or 14%.

8. The method of any one of claims 1-7, wherein the antibody is a non-functional antibody; and/or wherein the drug concentration varies within the antibody specification concentration.

9. The method of any one of claims 1-8, wherein the antibody concentration and the drug concentrations are allowed to vary.

10. A method of preparing a pharmaceutical composition comprising:
    (a) measuring the drug concentration in a composition comprising an antibody drug conjugate; and
    (b) formulating the composition comprising an antibody drug conjugate composition to achieve the drug concentration falling within ± 10% of a targeted drug concentration; wherein said formulating step (b) does not include formulating said composition comprising an antibody drug conjugate to achieve a targeted antibody concentration.

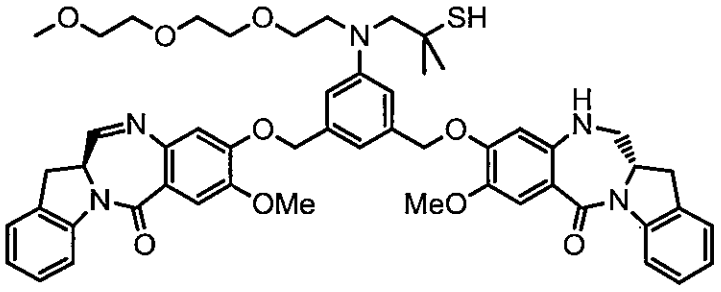
11. The method of any one of claims 1-10, wherein the drug is a tubulin inhibitor, DNA damaging agent, DNA cross linker, DNA alkylating agent, cell cycle disrupter; a maytansinoid; a benzodiazepine compound; pyrrolobenzodiazepine; indolinobenzodiazepine; or an auristatin.

12. The method of any one of claims 8-11, wherein the antibody is a non-functional antibody.

13. The method of any one of claims 1-12, wherein the drug is a benzodiazepine compound and the antibody is a non-functional antibody; or wherein the drug is a maytansinoid and the antibody is a non-functional antibody.

14. The method of claim 13, wherein the antibody drug conjugate is huMov19-sulfo-SPDB-$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl) maytansine (DM4) or huMy9-6-sulfo-

SPDB-DGN462, wherein DGN42 comprises the structure



15. The method of any one of claims 1-7 and 9-11, wherein the antibody is a functional antibody.

16. The method of any one of claims 10-15, wherein the method reduces batch-to-batch potency variability in producing the pharmaceutical composition.

17. A method of reducing potency variability in a composition comprising an antibody benzodiazepine conjugate, the method comprising:
    (a) measuring the DAR for the antibody benzodiazepine conjugate composition;
    (b) determining the upper antibody specification limit and the lower antibody specification limit, wherein the upper antibody specification limit is the target antibody concentration plus the maximum variation allowed by the specification and the lower antibody specification limit is the target antibody concentration minus the maximum variation allowed by the specification;
    (c) determining the defined upper benzodiazepine specification limit and the defined lower benzodiazepine specification limit, wherein the defined upper benzodiazepine specification limit is the target benzodiazepine concentration plus the maximum variation allowed by the specification and the defined lower benzodiazepine specification limit is the target benzodiazepine concentration minus the maximum variation allowed by the specification;
    (d) determining the calculated upper benzodiazepine specification limit (USL (drug)) as follows:

USL (drug) μg/mL= Upper Antibody Concentration Specification Limit x DAR x Drug Mol. Wt. x 1000
Antibody Mol. Wt.

(e) determining the calculated lower benzodiazepine specification limit (LSL (drug)) as follows:

LSL (drug) μg/mL= Lower Antibody Concentration Specification Limit x DAR x Drug Mol. Wt .x 1000
Antibody Mol. Wt.

(f) comparing the calculated USL (drug) of step (d) to the defined upper benzodiazepine specification limit of step (c), and selecting the lower of the two values as the effective upper benzodiazepine specification limit;

(g) comparing the calculated LSL (drug) of step (e) to the defined lower benzodiazepine specification limit of step (c), and selecting the higher of the two values as the effective lower benzodiazepine specification limit; and

(h) formulating the antibody benzodiazepine conjugate composition to a target benzodiazepine concentration that is the midpoint between the effective upper benzodiazepine specification limit and the effective lower benzodiazepine specification limit, thereby reducing potency variability in said composition.

18. The method of claim 17, wherein the method narrows the range of the upper and lower specification limits for the drug and the antibody to ± 3-5%;

optionally wherein the method narrows the range of the upper and lower specification limits to ± 4%.

19. The method of claim 17, wherein the maximum variation allowed by the specification in step (b) is ± 15%;

optionally wherein the maximum variation allowed by the specification in step (b) is less than 10, 11, 12, 13, or 14%.

20. The method of claim 17, wherein the maximum variation allowed by the specification in step (c) is ± 15%;

optionally wherein the maximum variation allowed by the specification in step (c) is less than 10, 11, 12, 13, or 14%.

21. The method of any one of claims 16-20, wherein the antibody is a non-functional antibody.

22. The method of any one of claims 4-9 and 17-21, wherein the DAR is at the lower limit of DAR specification or at the upper limit of DAR specification;

optionally wherein the lower limit of DAR specification is 2.3, 2.4, or 2.5; and/or

optionally wherein the upper limit of DAR specification is 2.9, 3.0, or 3.1.

23. The method of any one of claims 1-22, wherein the composition varies in potency by 10-40%;

optionally wherein the composition varies in potency by 10-20%, or optionally wherein the composition varies in potency by 20%.

24. The method of any one of claims 1-23, wherein variability in composition potency is reduced relative to when the antibody drug conjugate composition is formulated based on antibody concentration alone;

optionally wherein the antibody concentration and drug concentration are determined by spectrophotometric measurement;

optionally wherein drug to antibody ratio is determined by size exclusion chromatography (SEC) or SEC-mass spectrometry (SEC-MS);

optionally wherein the antibody drug conjugate composition is formulated for infusion;

optionally wherein the antibody drug conjugate is formulated with a pharmaceutically acceptable parenteral vehicle; or

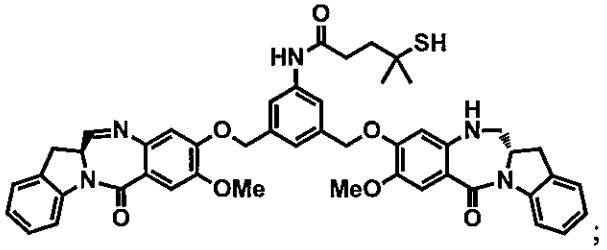
optionally wherein the antibody drug conjugate is formulated in a unit dosage injectable form.

25. The method of any one of claims 11-16 and 21-24, wherein the maytansinoid is DM1, DM3, or DM4.

26. The method of any one of claims 22-25, wherein the antibody is a non-functional antibody; optionally wherein the non-functional antibody is huMov19, huMy9-6, huB4, or huDS6.

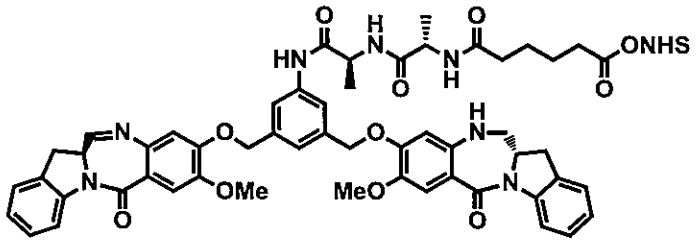
27. The method of any one of claims 1, 4, 10, 16, and 17, wherein the antibody drug conjugate is huMov19-sulfo-SPDB-DM4, huMov19-sulfo-SPDB-D1, huMov19-D2, huMov19-sulfo-SPDB-D10, huMov19-sulfo-SPDB-DGN462, huMy9-6-sulfo-SPDB-D1, huMy9-6-D2, huMy9-6-sulfo-SPDB-D10, huMy9-6-sulfo-SPDB-DGN462, huAnti-CD123-sulfo-SPDB-D1, huAnti-CD123-D2, huAnti-CD123-sulfo-SPDB-D10, huAnti-CD123-sulfo-SPDB-DGN462, huB4-SPDB-DM4, huDS6-SPDB-DM4, huCD37-3-SMCC-DM1, huCD37-50-SMCC-DM1, or huEGFR-7R-SMCC-DM1,

wherein D1 comprises the structure



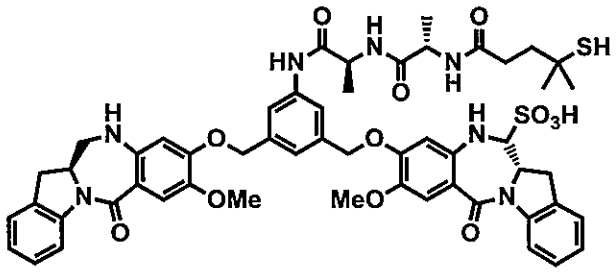
;

wherein D2 comprises the structure



; and

wherein D10 comprises the structure



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28. Use of an antibody drug conjugate composition formulated according to the method of any one of claims 1-26 in the preparation of a medicament for the treatment of a cancer.

29. Use of a pharmaceutical composition comprising an huMov19-sulfo-SPDB-DM4 antibody drug conjugate formulated according to the method of any one of claims 1-12, 16, and 21-27 in the preparation of a medicament for the treatment of a cancer, wherein a nominal maytansinoid concentration is recited on a label.

30. Use of a pharmaceutical composition comprising an huMy9-6-sulfo-SPDB-DGN462 antibody drug conjugate formulated according to the method of any one of claims 1-14, 17-24, 26, and 27 in the preparation of a medicament for the treatment of a cancer, wherein a nominal DGN462 concentration is recited on a label.

31. The method of any one of claims 1-26, further comprising measuring the antibody concentration to determine the drug antibody ratio (DAR) of the pharmaceutical composition.

32. The method of any one of claims 1-14, 16-26 and 31, wherein the antibody drug conjugate comprises an antibody comprising light chain CDR sequences comprising the amino acid sequences set forth in amino acids 24-38 of SEQ ID NO:4, amino acids 54-60 of SEQ ID NO:4, and amino acids 93-101 of SEQ ID NO:4 and heavy chain CDR sequences comprising the amino acid sequences set forth in amino acids 31-35 of SEQ ID NO:5, amino acids 50-66 of SEQ ID NO:5, and amino acids 99-107 of SEQ ID NO:5.

33. The method of any one of claims 1-14, 16-26, 31, and 32, wherein the antibody drug conjugate comprises an antibody comprising a light chain comprising the amino acid sequence set forth in SEQ ID NO:4 and a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:5.

34. The method of any one of claims 1-14, 16-26 and 31, wherein the antibody drug conjugate comprises an antibody comprising light chain CDR sequences comprising the amino acid sequences set forth in amino acids 24-39 of SEQ ID NO:8, amino acids 56-62 of SEQ ID NO:8, and amino acids 95-102 of SEQ ID NO:8 and heavy chain CDR sequences comprising

the amino acid sequences set forth in amino acids 31-35 of SEQ ID NO:9, amino acids 50-65 of SEQ ID NO:9, and amino acids 99-107 of SEQ ID NO:9.

35. The method of any one of claims 1-14, 16-26, 31, and 34, wherein the antibody drug conjugate comprises an antibody comprising a light chain comprising the amino acid sequence set forth in SEQ ID NO:8 and a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:9.