CLAIMS

We claim:

1. A stable aqueous pharmaceutical formulation, the formulation comprising a therapeutically effective amount of an antibody in an arginine buffer, pH 4.0 to 6.0.

2. The formulation of claim 1, wherein the buffer is an arginine acetate buffer, pH 4.5 to 5.5.

3. The formulation of claim 1, wherein the buffer is an arginine acetate buffer, pH 4.8 to 5.4.

4. The formulation of claim 1, wherein the buffer is an arginine acetate buffer, pH 5.2.

5. The formulation of claims 2, 3, or 4 wherein the arginine actetate concentration in the buffer is from about 25 mM to about 250 mM.

6. The formulation of claims 2, 3, or 4 wherein the arginine actetate concentration in the buffer is from about 50 mM to about 250 mM.

7. The formulation of claims 2, 3, or 4 wherein the arginine actetate concentration in the buffer is from about 75 mM to about 250 mM.

8. The formulation of claims 2, 3, or 4 wherein the arginine actetate concentration in the buffer is from about 100 mM to about 250 mM.

9. The formulation of claims 2, 3, or 4, wherein the arginine acetate concentration in the buffer is from about 120 mM to about 240 mM.

10. The formulation of claims 2, 3, or 4, wherein arginine acetate concentration in the buffer is from about 150 mM to about 225 mM.

11. The formulation of claims 2, 3, or 4, wherein the arginine acetate concentration in the buffer is about 200 mM.

12. The formulation of claim 1, further comprising a surfactant.

13. The formulation of claim 12, wherein the surfactant is polysorbate.

14. The formulation of claim 13, wherein the polysorbate is polysorbate 20.

15. The formulation of claim 12, wherein the surfactant concentration is from 0.0001% to about 1.0%.

16. The formulation of claim 12, wherein the surfactant concentration is from about 0.01% to about 0.05%.

17. The formulation of claim 12, wherein the surfactant concentration is 0.04%.

18. The formulation of claim 1, wherein the antibody concentration is from about 10 mg/ml to about 250 mg/ml.

19. The formulation of claim 1, wherein the antibody concentration is from about 25 mg/ml to 200 mg/ml.

20. The formulation of claim 1, wherein the antibody concentration is from about 50 mg/ml to about 150 mg/ml.

21. The formulation of claim 1, wherein the antibody concentration is from about 75 mg/ml to about 125 mg/ml.

22. The formulation of claim 1, wherein the antibody is not subject to prior lyophilization.

23. The formulation of claim 1 wherein the antibody binds VEGF.

24. The formulation of claim 1, wherein the antibody is a monoclonal antibody.

25. The formulation of claim 24 wherein the monoclonal antibody is a full length antibody.

26. The formulation of claim 24 wherein the monoclonal antibody is an IgG1 antibody.

27. The formulation of claim 24 wherein the monoclonal antibody is a humanized antibody.

28. The formulation of claim 24 wherein the monoclonal antibody is an antibody fragment comprising an antigen-binding region.

29. The formulation of claim 28 wherein the antibody fragment is a Fab or F(ab')2 fragment.

30. The formulation of claim 24 wherein the monoclonal antibody binds VEGF.

31. The formulation of claim 30 wherein the antibody is bevacizumab.

32. The formulation of claim 1 wherein the monoclonal antibody is susceptible to aggregation.

33. The formulation of claim 2 wherein the buffer is 200 mM arginine acetate pH 5.2, the surfactant is polysorbate in an amount of about 0.01-0.1% v/v, wherein the formulation is stable at a temperature of about 40°C for at least 28 days

34. An article of manufacture comprising a container holding a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody, an arginine acetate buffer from about pH 4.5 to about 6.0, and a surfactant.

35. The article of manufacture of claim 34, wherein the antibody binds VEGF.

36. The article of manufacture of claim 35, wherein the antibody is bevacizumab.

37. A method for stabilizing an antibody in an aqueous pharmaceutical formulation by combining a therapeutically effective amount of an antibody, an arginine acetate buffer from about pH 4.5 to about 6.0, and a surfactant.

38. The method of claim 37, wherein the antibody binds VEGF.

39. The method of claim 38, wherein the antibody is bevacizumab.

40. A stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody, 200 mM arginine acetate buffer at pH 5.2, and a surfactant.

41. The formulation of claim 40 wherein the antibody binds VEGF.

42. The formulation of claim 41 wherein the antibody is bevacizumab

43. An article of manufacture comprising a container holding the formulation of any one of claims 40-42.

44. The formulation of claim 1 which is sterile.

45. The formulation of claim 1 which is stable upon storage at about 40°C for at least 28 days.

46. The formulation of claim 1 which is aqueous and is administered to a subject.

47. The formulation of claim 46 wherein the formulation is for intravenous (IV), subcutaneous (SQ) or intramuscular (IM) administration.

48. The formulation of claim 46, which is for IV administration and the antibody concentration is from about 10 mg/ml to about 250 mg/ml.

49. The formulation of claim 46, which is for IV administration and the antibody concentration is from about 50 mg/ml to about 100 mg/ml.

50. The formulation of claim 46, which is for SQ administration and the antibody concentration is from about 25 mg/ml to about 250 mg/ml.

51. The formulation of claim 46, which is for SQ administration and the antibody concentration is from about 50 mg/ml to about 100 mg/ml.

52. A vial with a stopper pierceable by a syringe comprising the formulation of claim 1 inside the vial.

53. The vial of claim 52 which is stored at about 2-8°C.

54. The vial of claim 52 which is a 3cc, 20 cc or 50 cc vial.

55. A stainless steel tank comprising the formulation of claim 1 inside the tank.

56. The tank of claim 55 wherein the formulation is frozen.

57. A method of treating a disease or disorder in a subject comprising administering the formulation of claim 1 to a subject in an amount effective to treat the disease or disorder.

58. The method of claim 57 wherein the antibody binds VEGF.

59. The method of claim 58 wherein the antibody is bevacizumab

60. A pharmaceutical formulation comprising: (a) a full length IgG1 antibody susceptible to deamidation or aggregation in an amount from about 10 mg/mL to about 250 mg/mL; (b) arginine acetate buffer, pH 4.5 to 6.0; and (c) polysorbate 20 in an amount from about 0.01% to about 0.1%.

61. The formulation of claim 60 wherein the antibody binds VEGF.

62. The formulation of claim 61 wherein the antibody is bevacizumab

63. A method for reducing aggregation of a therapeutic monoclonal antibody, comprising formulating the antibody in an arginine acetate buffer, pH 4.5 to 6.0.

64. The method of claim 63 wherein the antibody binds VEGF.

65. The method of claim 64 wherein the antibody is bevacizumab.

66. A pharmaceutical formulation comprising an antibody that binds to VEGF in an arginine acetate buffer at a pH from about 4.5 to about 6.0, and a surfactant.

67. The formulation of claim 66 wherein the antibody is bevacizumab.

68. A method of making a pharmaceutical formulation comprising:

(a) preparing the formulation of claim 1; and

(b) evaluating physical stability, chemical stability, or biological activity of the antibody in the formulation.

69. The method of claim 68, wherein the antibody binds VEGF.

70. The method of claim 69, wherein the antibody is bevacizumab

CLAIMS

We claim:

1. A pharmaceutical formulation comprising an antibody that binds to VEGF in an arginine acetate buffer at a pH from 4.5 to 6.0, and a surfactant, wherein the antibody is bevacizumab.

2. The pharmaceutical formulation of claim 1, wherein the arginine acetate buffer is pH 4.5 to 5.5.

3. The pharmaceutical formulation of claim 1 or 2, wherein the arginine acetate buffer is pH 4.8 to 5.4.

4. The pharmaceutical formulation of any one of claims 1-3, wherein the arginine acetate buffer is pH 5.2.

5. The pharmaceutical formulation of any one of claims 1-4, wherein the arginine acetate concentration in the buffer is from 25 mM to 250 mM.

6. The pharmaceutical formulation of any one of claims 1-5, wherein the arginine acetate concentration in the buffer is from 50 mM to 250 mM.

7. The pharmaceutical formulation of any one of claims 1-6, wherein the arginine acetate concentration in the buffer is from 75 mM to 250 mM.

8. The pharmaceutical formulation of any one of claims 1-7, wherein the arginine acetate concentration in the buffer is from 100 mM to 250 mM.

9. The pharmaceutical formulation of any one of claims 1-8, wherein the arginine acetate concentration in the buffer is from 120 mM to 240 mM.

10. The pharmaceutical formulation of any one of claims 1-9, wherein arginine acetate concentration in the buffer is from 150 mM to 225 mM.

11. The pharmaceutical formulation of any one of claims 1-10, wherein the arginine acetate concentration in the buffer is 200 mM.

12. The pharmaceutical formulation of any one of claims 1-11, wherein the surfactant is polysorbate.

13. The pharmaceutical formulation of claim 12, wherein the polysorbate is polysorbate 20.

14. The pharmaceutical formulation of any one of claims 1-13, wherein the surfactant concentration is from 0.0001% to 1.0% v/v.

15. The pharmaceutical formulation of any one of claims 1-14, wherein the surfactant concentration is from 0.01% to 0.05% v/v.

16. The pharmaceutical formulation of any one of claims 1-15, wherein the surfactant concentration is 0.04% v/v.

17. The pharmaceutical formulation of any one of claims 1-16, wherein the antibody concentration is from 10 mg/ml to 250 mg/ml.

18. The pharmaceutical formulation of any one of claims 1-17, wherein the antibody concentration is from 25 mg/ml to 200 mg/ml.

19. The pharmaceutical formulation of any one of claims 1-18, wherein the antibody concentration is from 50 mg/ml to 150 mg/ml.

20. The pharmaceutical formulation of any one of claims 1-19, wherein the antibody concentration is from 75 mg/ml to 125 mg/ml.

21. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody is not subject to prior lyophilization.

22. The pharmaceutical formulation of any one of claims 1-21 which is sterile.

23. The pharmaceutical formulation of any one of claims 1-22 which is stable upon storage at 40°C for at least 28 days.

24. The pharmaceutical formulation of any one of claims 1-23 which is aqueous and is to be administered to a subject.

25. The pharmaceutical formulation of any one of claims 1-24, wherein the pharmaceutical formulation is for intravenous (IV), subcutaneous (SQ) or intramuscular (IM) administration.

26. The pharmaceutical formulation of 25, which is for IV administration and the antibody concentration is from 10 mg/ml to 250 mg/ml.

27. The pharmaceutical formulation of claim 26, which is for IV administration and the antibody concentration is from 50 mg/ml to 100 mg/ml.

28. The pharmaceutical formulation of claim 25, which is for SQ administration and the antibody concentration is from 25 mg/ml to 250 mg/ml.

29. The pharmaceutical formulation of claim 28, which is for SQ administration and the antibody concentration is from 50 mg/ml to 100 mg/ml.

30. The pharmaceutical formulation of claim 1, wherein the antibody concentration is 75 mg/ml to 100 mg/ml, the arginine acetate buffer is pH 4.8 to 5.4, the arginine acetate concentration in the buffer is from 150 mM to 225 mM, and the polysorbate 20 concentration is from 0.01 to 0.05% v/v.

31. The pharmaceutical formulation of claim 30, wherein the antibody concentration is 100 mg/ml, the arginine acetate buffer is pH 5.2, the arginine acetate concentration in the buffer is 200 mM, and the polysorbate 20 concentration is 0.04% v/v.

32. An article of manufacture comprising the pharmaceutical formulation of any one of claims 1-31.

33. A method for reducing aggregation of a therapeutic monoclonal antibody, comprising formulating the antibody in an arginine acetate buffer, pH 4.5 to 6.0, wherein the antibody is bevacizumab.

34. The method of claim 33, wherein the buffer is an arginine acetate buffer, pH 4.5 to 5.5.

35. The method of claim 33 or 34, wherein the buffer is an arginine acetate buffer, pH 4.8 to 5.4.

36. The method of any one of claims 33-35, wherein the buffer is an arginine acetate buffer, pH 5.2.

37. The method of any one of claims 33-36, wherein the arginine acetate concentration in the buffer is from 25 mM to 250 mM.

38. The method of any one of claims 33-37, wherein the arginine acetate concentration in the buffer is from 50 mM to 250 mM.

39. The method of any one of claims 33-38, wherein the arginine acetate concentration in the buffer is from 75 mM to 250 mM.

40. The method of any one of claims 33-39, wherein the arginine acetate concentration in the buffer is from 100 mM to 250 mM.

41. The method of any one of claims 33-40, wherein the arginine acetate concentration in the buffer is from 120 mM to 240 mM.

42. The method of any one of claims 33-41, wherein arginine acetate concentration in the buffer is from 150 mM to 225 mM.

43. The method of any one of claims 33-42, wherein the arginine acetate concentration in the buffer is 200 mM.

44. The method of claim 33, wherein the formulation further comprises a surfactant.

45. The method of claim 44, wherein the surfactant is polysorbate.

46. The method of claim 45, wherein the polysorbate is polysorbate 20.

47. The method of any one of claims 44-46, wherein the surfactant concentration is from 0.0001% to 1.0% v/v.

48. The method of any one of claims 44-47, wherein the surfactant concentration is from 0.01% to 0.05% v/v.

49. The method of any one of claims 44-48, wherein the surfactant concentration is 0.04% v/v.

50. The method of any one of claims 33-49, wherein the antibody concentration is from 10 mg/ml to 250 mg/ml.

51. The method of any one of claims 33-50, wherein the antibody concentration is from 25 mg/ml to 200 mg/ml.

52. The method of any one of claims 33-51, wherein the antibody concentration is from 50 mg/ml to 150 mg/ml.

53. The method of any one of claims 33-52, wherein the antibody concentration is from 75 mg/ml to 125 mg/ml.

54. The method of any one of claims 33-53, wherein the antibody is not subject to prior lyophilization.

55. A vial with a stopper pierceable by a syringe comprising the pharmaceutical formulation of any one of claims 1-31 inside the vial.

56. The vial of claim 55 which is stored at 2-8°C.

57. The vial of claim 55 or 56 which is a 3 cc, 20 cc or 50 cc vial.

58. The vial of any one of claims 55-57, wherein the antibody concentration in the formulation is 75 mg/ml to 100 mg/ml, the arginine acetate buffer is pH 4.8 to 5.4, the arginine acetate concentration in the buffer is from 150 mM to 225 mM, and the surfactant is polysorbate 20 at a concentration from 0.01 to 0.05% v/v.

59. The vial of any one of claims 55-58, wherein the antibody concentration in the formulation is 100 mg/ml, the arginine acetate buffer is pH 5.2, the arginine acetate concentration in the buffer is 200 mM, and the polysorbate 20 concentration is 0.04% v/v.

60. A stainless steel tank comprising the pharmaceutical formulation of any one of claims 1-31 inside the tank.

61. The tank of claim 60 wherein the pharmaceutical formulation is frozen.

62. The tank of claim 60 or 61, wherein the antibody concentration in the formulation is 75 mg/ml to 100 mg/ml, the arginine acetate buffer is pH 4.8 to 5.4, the arginine acetate concentration in the buffer is from 150 mM to 225 mM, and the surfactant is polysorbate 20 at a concentration from 0.01 to 0.05% v/v.

63. The tank of any one of claims 60-62, wherein the antibody concentration in the formulation is 100 mg/ml, the arginine acetate buffer is pH 5.2, the arginine acetate concentration in the buffer is 200 mM, and the polysorbate 20 concentration is 0.04% v/v.

64. Use of a pharmaceutical formulation of any one of claims 1-31 in the manufacture of a medicament for treating a disease or disorder in a subject.

65. The use of claim 64, wherein the disease or disorder is cancer.

66. The use of claim 65, wherein the cancer is colorectal cancer, lung cancer, breast cancer, renal cancer, or glioblastoma.