CLAIMS

WHAT IS CLAIMED IS:

1. An aqueous, buffered pharmaceutical composition comprising adalimumab and a buffer, wherein (i) the composition is free or substantially free of a buffer combination that comprises both a citrate buffer and a phosphate buffer; and (ii) the composition exhibits long term stability.

2. The composition of claim 1 comprising at least one buffer selected from the group consisting of histidine, succinate, phosphate, citrate, acetate, maleate and tartrate buffers, including combinations thereof, provided such combinations do not include a combination of citrate buffer and phosphate buffer.

3. The composition of claim 1 wherein the buffer comprises histidine.

4. The composition of claim 1 wherein the buffer comprises succinate.

5. The composition of claim 1 wherein the buffer comprises a combination of succinate buffer and histidine buffer.

6. The composition of claim 2 free or substantially free of citrate buffer.

7. The composition of claim 6 in which the sole buffer present therein is either (i) a histidine buffer; (ii) a succinate buffer; or (iii) a buffer combination consisting essentially of histidine buffer and succinate buffer.

8. The composition of claim 1 further comprising a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof.

9. The composition of claim 8 wherein the stabilizer comprises glycine.

10. The composition of claim 8 wherein the stabilizer comprises arginine.

11. The composition of claim 8 wherein the stabilizer comprises a combination of glycine and arginine.

12. The composition of claim 1 further comprising a polyol selected from the group consisting of mannitol, sorbitol and trehalose.

13. The composition of claim 1 further comprising a polysorbate or poloxamer surfactant.

14. The composition of claim 1 free or substantially free of polyol.

15. The composition of claim 1 free or substantially free of surfactant.

16. The composition of claim 1 free or substantially free of both surfactant and polyol.

17. The composition of claim 1 comprising (i) a histidine buffer, or a succinate buffer, or combination thereof; (ii) a polysorbate or poloxamer surfactant, or combination thereof; and (iii) one or both of the following:

    (a) a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof; and

    (b) a polyol selected from sorbitol, mannitol, and trehalose, or combinations thereof.

18. The composition of claim 17 comprising (a) and not (b).

19. The composition of claim 17 comprising (b) and not (a).

20. The composition of claim 17 comprising (a) and (b).

21. The composition of claim 17, in which (i) histidine buffer, succinate buffer, or combinations of thereof constitute essentially the sole buffers in the composition; (ii); the stabilizer (if present) comprises glycine, arginine or combinations thereof; (iii) the polyol (if present) comprises mannitol; and (iv) the surfactant comprises at least one member of the group consisting of PS 80, PS 40, PS20, Pluronic F-68 and combinations thereof.

22. The composition of claim 21 in which the stabilizer further comprises up to about 100 mM sodium chloride.

23. The composition of claim 17 wherein the stabilizers may optionally include sucrose.

24. The composition of claim 21 wherein the amount of adalimumab is about 50 to about 150 mg/ml; the amount of buffer is up to about 50 mM; the amount of stabilizer (if present) is up to about 300 mM; the amount of polyol (if present) is up to about 300 mM; and the amount of surfactant is in the range of about 0.01 to about 0.1 wt.%.

25. The composition of claim 24, in which the stabilizer is not present.

26. The composition of claim 23, in which the amount of polyol is present in an amount approximately at or greater than about 200 mM.

27. The composition of claim 24 in which the polyol is not present.

28. The composition of claim 23 in which both the polyol and the stabilizer are present, and wherein the combined amount of the stabilizer and the polyol is about 150 to 300 mM.

29. An aqueous, buffered pharmaceutical composition exhibiting long term stability, said composition comprising: (i) adalimumab; (ii) a buffer selected from the group consisting of histidine buffer, succinate buffer, and combinations thereof; (iii) a polysorbate or poloxamer surfactant, or combinations thereof; and (iv) one or both of the following:

    (a) a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof; and

    (b) a polyol selected from sorbitol, mannitol, and trehalose, or combinations thereof.

30. The composition of claim 29 further comprising a buffer selected from the group consisting of phosphate, citrate, acetate, maleate and tartrate buffers, including combinations thereof.

31. The composition of claim 29 wherein the composition does not contain a buffer combination comprising a citrate buffer and a phosphate buffer.

32. The composition of claim 29 wherein the composition does not contain a citrate buffer and, optionally, wherein histidine buffer, or the combination of histidine and succinate buffer, is/are present as essentially the sole buffer(s) in the composition.

33. The composition of claim 29 comprising (a) and not (b).

34. The composition of claim 29 comprising (b) and not (a).

35. The composition of claim 29 comprising (a) and (b).

36. The composition of claim 29, in which (i); the stabilizer (if present) comprises glycine, arginine or combinations thereof; (ii) the polyol (if present) comprises mannitol; and (iii) the surfactant comprises at least one member of the group consisting of PS 80, PS 40, PS20, Pluronic F-68 and combinations thereof.

37. The composition of claim 36 in which the stabilizer further comprises up to about 100 mM sodium chloride.

38. The composition of claim 36 wherein the amount of adalimumab is about 50 to about 150 mg/ml; the amount of buffer is up to about 50 mM; the amount of stabilizer (if present) is up to about 300 mM; the amount of polyol (if present) is up to about 300 mM; and the amount of surfactant is in the range of about 0.01 to about 0.1 wt.%

39. The composition of claim 38, in which the stabilizer is not present.

40. The composition of claim 39, in which the polyol is present in an amount approximately at or greater than about 200 mM.

41. The composition of claim 38 in which both the polyol and the stabilizer are present, and wherein the combined amount of the stabilizer and the polyol is about 150 to 300 mM.

42. The composition of claim 30 free or substantially free of either (i) citrate buffer; or (ii) citrate/phosphate buffer combinations.

43. The composition of claim 38 containing the stabilizer but not the polyol.

44. An aqueous, buffered pharmaceutical composition comprising adalimumab and a buffer, wherein (i) the composition is free or substantially free of a polyol; and (ii) the composition exhibits long term stability.

45. The composition of claim 44 comprising at least one buffer selected from the group consisting of histidine, succinate, phosphate, citrate, acetate, maleate and tartrate buffers, including combinations thereof.

46. The composition of claim 45 wherein the buffer comprises histidine.

47. The composition of claim 45 wherein the buffer comprises succinate.

48. The composition of claim 45 wherein the buffer comprises a combination of succinate buffer and histidine buffer.

49. The composition of claim 45 in which essentially the sole buffer present therein is either (i) a histidine buffer; (ii) a succinate buffer; or (iii) a buffer combination consisting essentially of histidine buffer and succinate buffer.

50. The composition of claim 45 further comprising a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof.

51. The composition of claim 50 wherein the stabilizer comprises glycine.

52. The composition of claim 50 wherein the stabilizer comprises arginine.

53. The composition of claim 50 wherein the stabilizer comprises a combination of glycine and arginine.

54. The composition of claim 45 further comprising a polysorbate or poloxamer surfactant.

55. The composition of claim 44 comprising (i) a histidine buffer or succinate buffer, or combinations thereof; (ii) a polysorbate or poloxamer surfactant, or combinations thereof; and (iii) a stabilizer selected from glycine, arginine, methionine, EDTA, sodium chloride, and combinations thereof.

56. The composition of claim 55, in which (i) histidine buffer, succinate buffer, or combinations thereof constitute essentially the sole buffers in the composition; (ii); the stabilizer comprises glycine, arginine or combinations thereof; and (iii) the surfactant comprises at least one member of the group consisting of PS 80, PS 40, PS20, Pluronic F-68 and combinations thereof.

57. The composition of claim 56 in which the stabilizer further comprises up to about 100 mM sodium chloride.

58. The composition of claim 56 wherein the amount of adalimumab is about 50 to about 150 mg/ml; the amount of buffer is up to about 50 mM; the amount of stabilizer is up to about 300 mM; and the amount of surfactant is in the range of about 0.01 to about 0.1 wt.%.

59. The composition of claim 45, free or substantially free of either (i) citrate buffer; or (ii) citrate/phosphate buffer combinations.

60. The composition of claim 45 free or substantially free of surfactant.

61. An aqueous, buffered pharmaceutical composition comprising adalimumab and a buffer, wherein (i) the composition is free or substantially free of surfactant; and (ii) the composition exhibits long term stability.

62. The composition of claim 61 comprising at least one buffer selected from the group consisting of histidine, succinate, phosphate, citrate, acetate, maleate and tartrate buffers, including combinations thereof.

63. The composition of claim 62 wherein the buffer comprises histidine.

64. The composition of claim 62 wherein the buffer comprises succinate.

65. The composition of claim 62 wherein the buffer comprises a combination of succinate buffer and histidine buffer.

66. The composition of claim 62 in which essentially the sole buffer present therein is either (i) a histidine buffer; (ii) a succinate buffer; or (iii) a buffer combination consisting essentially of histidine buffer and succinate buffer.

67. The composition of claim 62 further comprising a a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof.

68. The composition of claim 67 wherein the stabilizer comprises glycine.

69. The composition of claim 67 wherein the stabilizer comprises arginine.

70. The composition of claim 67 wherein the stabilizer comprises a combination of glycine and arginine.

71. The composition of claim 61 further comprising a polyol.

72. The composition of claim 62 comprising (i) a histidine buffer or succinate buffer, or combinations thereof; and one or both of the following:

(a) a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof; and/or

(b) a polyol selected from sorbitol, mannitol, and trehalose, or combinations thereof.

73. The composition of claim 72 comprising (a) and not (b).

74. The composition of claim 72 comprising (b) and not (a).

75. The composition of claim 72 comprising (a) and (b).

76. The composition of claim 72, in which (i) histidine buffer, succinate buffer, or combinations of thereof constitute essentially the sole buffers in the composition; (ii); the stabilizer (if present) comprises glycine, arginine or combinations thereof; and (iii) the polyol (if present) comprises mannitol.

77. The composition of claim 76 in which the stabilizer further comprises up to about 100 mM sodium chloride.

78. The composition of claim 76 wherein the amount of adalimumab is about 50 to about 150 mg/ml; the amount of buffer is up to about 50 mM; the amount of stabilizer (if present) is up to about 300 mM; and the amount of polyol (if present) is up to about 300 mM.

79. The composition of claim 61 free or substantially free of either (i) citrate buffer; or (ii) citrate/phosphate buffer combinations.

80. The composition of claim 62 free or substantially free of poyol.

81. An aqueous pharmaceutical composition comprising adalimumab wherein: (i) the composition is free or substantially free of buffer; and (ii) the composition exhibits long term stability.

82. The composition of claim 81 further comprising one or both of the following:

(a) a stabilizer selected from the group consisting of glycine, alanine, glutamate, arginine, methionine, EDTA, sodium chloride, sodium sulfate, metal ions, and combinations thereof; and/or

(b) a polyol selected from sorbitol, mannitol, and trehalose, or combinations thereof.

83. The composition of claim 82 comprising (a) and not (b).

84. The composition of claim 82 comprising (b) and not (a).

85. The composition of claim 82 comprising (a) and (b).

86. The composition of claim 82 wherein the stabilizer (if present) comprises glycine, arginine, or a combination thereof.

87. The composition of claim 82 wherein the polyol (if present) comprises mannitol.

88. The composition of claim 82 wherein the amount of adalimumab is about 50 to about 150 mg/ml; the amount of stabilizer is up to about 300 mM; and the amount of polyol (if present) is up to about 300 mM.

89. The composition of claim 82 wherein the combined amount of stabilizer and polyol is in the range of about 150 to 300 mM.

90. A method for enhancing long term stability in an aqueous, buffered adalimumab formulation, comprising one or more of the steps of:

(a) incorporating histidine buffer, succinate buffer, or a combination thereof, in the formulation based on empirical data indicating that such buffers contribute to the stability of the formulation to a greater extent than other buffers or buffer combinations; or

(b) incorporating glycine, arginine or a combination thereof as stabilizers in the formulation, based upon empirical data indicating that such stabilizer contribute to the stability of the formulation to a greater extent than other stabilizers; or

(c) substantially excluding the presence of buffer or buffer combinations comprising citrate buffer, based upon empirical data indicating that such buffer or buffer combinations perform poorly in terms of stabilizing the formulation in comparison to other buffers.

91. The method of claim 90, wherein the resulting formulation exhibits long term stability comparable to or better than commercially available adalimumab formulations marketed under the trademark Humira®.

92. A formulation of adalimumab exhibiting long term stability consisting of, or consisting essentially of: adalimumab, histidine buffer, glycine and polysorbate 80.

93. A formulation of adalimumab exhibiting long term stability consisting of, or consisting essentially of: adalimumab, histidine buffer, mannitol and polysorbate 80.

CLAIMS

1. An aqueous, buffered pharmaceutical composition comprising adalimumab and a buffer, wherein (i) the composition is free or substantially free of a buffer combination that comprises both a citrate buffer and a phosphate buffer; and (ii) the composition exhibits long term stability.

2. The composition of claim 1 wherein a histidine buffer, or the combination of a histidine buffer and succinate buffer, constitute essentially the sole buffers in the composition; and the composition comprises: 50 to 150 mg of adalimumab, and at least one of the following: (i) up to 300 mM of at least one stabilizer selected from glycine and arginine; (ii) up to 300 mM of at least one polyol selected from the group consisting of mannitol, sorbitol and trehalose.

3. The composition of claim 2 further comprising at least one of (a) 0.01 to 0.1 wt% of a polysorbate or poloxamer surfactant; and (b) up to 150 mM sodium chloride.

4. The composition of claim 3 wherein the buffer consists of, or consists essentially of, histidine buffer, and the composition comprises said surfactant and either (a) both stabilizer and polyol; or (b) polyol or stabilizer, but not both.

5. The composition of claim 4 further comprising up to 100 mM sodium chloride.

6. An aqueous, buffered pharmaceutical composition, free or substantially free of citrate buffer, exhibiting long term stability, said composition comprising: (i) adalimumab; (ii) a histidine buffer; (iii) a polysorbate or poloxamer surfactant; and (iv) one or both of the following:

   (a) a stabilizer selected from glycine and arginine, and combinations thereof; and

   (b) a polyol selected from sorbitol, mannitol, and trehalose, and combinations thereof.

7. The composition of claim 6 comprising up to 100 mM sodium chloride.

8. The composition of claim 6 wherein the amount of adalimumab is 50 to 150 mg/ml; the buffer is present in an amount up to 50 mM; the amount of

stabilizer (if present) is up to 300 mM; the amount of polyol (if present) is up to 300 mM; and the amount of surfactant is 0.01 to 0.1 wt.%

9. The composition of claim 7 in which either the polyol is present; or the stabilizer is present; but not both.

10. The composition of claim 9 in which the polyol is present, but the stabilizer is absent.

11. The composition of claim 9 in which the stabilizer is present, but the polyol is absent.

12. An aqueous, buffered pharmaceutical composition comprising (a) adalimumab and (b) histidine as a sole buffer, wherein the composition further comprises at least one of the following: (i) a polyol selected from mannitol, sorbitol and trehalose or combinations thereof; (ii) a stabilizer selected from glycine and arginine or combinations thereof; and (iii) a surfactant selected from polysorbate and poloxamer surfactants or combination thereof.

13. The composition of claim 12 wherein the stabilizer is present; and the composition is free or substantially free of polyol.

14. The composition of claim 12 wherein the polyol is present and comprises mannitol; and the composition is free or substantially free of the stabilizer.

15. The composition of claim 12 wherein the polyol is present and comprises sorbitol; and the composition is free or substantially free of the stabilizer.

16. The composition of claim 12 wherein the stabilizer comprises glycine or arginine, but not both.

17. The composition of claim 12 wherein the stabilizer comprises up to 100 mM sodium choride.

18. The composition of claim 12 wherein the composition does not comprise both the stabilizer and the polyol.

19. A method for enhancing long term stability in an aqueous, buffered adalimumab formulation, comprising one or more of the steps of:

(a) incorporating histidine buffer, succinate buffer, or a combination thereof, in the formulation based on empirical data indicating that such buffers contribute to the stability of the formulation to a greater extent than other buffers or buffer combinations; or

(b) incorporating glycine, arginine or a combination thereof as stabilizers in the formulation, based upon empirical data indicating that such stabilizers contribute to the stability of the formulation to a greater extent than other stabilizers; or

(c) substantially excluding the presence of buffer or buffer combinations comprising citrate buffer, based upon empirical data indicating that such buffer or buffer combinations perform poorly in terms of stabilizing the formulation in comparison to other buffers.

20. A single dosage composition of adalimumab exhibiting long term stability consisting of, or consisting essentially of: (i) about 40 mg/ml adalimumab; (ii) buffer consisting solely of histidine; (iii) glycine; (iv) sodium chloride; and (v) polysorbate 80.