WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition stabilized for long term storage comprising etanercept and a stabilizer for preventing, inhibiting or reducing the occurrence of subvisible particles in the composition, wherein the stabilizer comprises a surfactant preferably selected from the group consisting of polysorbate surfactants and poloxamer surfactants, and capable of affording a significant reduction in sub-visible particles in the composition in comparison to an etanercept composition containing no surfactant; and wherein the composition is free, or essentially free of arginine as a stabilizer.

2. The stabilized composition of claim 1 wherein the stabilizer comprises a polysorbate surfactant selected from the group consisting of polysorbate 80, polysorbate 60, poysorbate 40 and polysorbate 20.

3. The stabilized composition of claim 2 wherein the stabilizer comprises polysorbate 80.

4. The stabilized composition of claim 1 wherein the stabilizer comprises a poloxamer surfactant, and the poloxamer surfactat is Pluronic F-68.

5. The stabilized composition of claim 1 wherein the composition is characterized by either (a) comprising an amount of sub-visible particles/ml of the composition having size of 1-10µm at "T0," where such amount of sub-visible particles corresponds to at least about a 50% to 70% reduction in such sub-visible particles in comparison to the same composition having no surfactant; and/or (b) comprising an amount of sub-visible particles in the formulation at "T0," such that the etanercept composition has (i) less than 2500 particles/ml having a size of 5-10µm; (ii) less than 3500 particles having size of about 2-5µm and (iii) less than 700 particles/ml having size of about 1-2 µm.

6. The stabilized composition of claim 5 comprising a further stabilizing ingredient, wherein said further stabilizing ingredient is selected from: (i) an amino acid selected from the group consisting of serine, proline and glutamate; (ii) a metal ion selected from the group consisting calcium,

magnesium and zinc; (iii) a xylitol stabilizer selected from xylitol, alone, or a combination of xylitol and meglumine; (iv) a sodium chloride stabilizer selected from sodium chloride alone; sodium chloride in combination with sucrose or trehalose, and the combination of sodium chloride, sucrose and trehalose; (v) a meglumine stabilizer selected from meglumine alone; meglumine in combination with sucrose; meglumine in combination with sodium chloride; and meglumine with sodium chloride and and sucrose; and (vi) the combination of a sugar and a polyol.

7. The stabilized composition of claim 6 wherein said further stabilizing ingredient is glutamate and the composition comprises: 25 to 75 mg/ml of etanercept; up to 150 mM glutamate; less than 6 wt% sucrose; optionally up to 100 mM NaCl; 1 to about 30 mM sodium phosphate, and 0.01 to 0.05 % (w/v) of the polysorbate or poloxomaer surfactant; wherein the composition has a pH of about 6.0 to 6.6.

8. The stabilized composition of claim 6 wherein said further stabilizing ingredient is serine and the composition comprises: 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; less than 150 mM serine; 0.5 to 3 wt% sucrose; 1 to 30 mM sodium phosphate, and wherein the formulation has pH 6.0 to pH 7.0.

9. The stabilized composition of claim 6 wherein said further stabilizing ingredient is proline and the composition comprises: 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; less than 150 mM proline; 0.5 to about 3 wt% sucrose; 1 to about 30 mM sodium phosphate, 15 to 100 mM NaCl; and wherein the formulation has pH 6.0 to pH 7.0.

10. The stabilized composition of claim 6 wherein the further stabilizing ingredient is magnesium chloride, and the composition comprises 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; 1 mM to 20 mM magnesium chloride; optionally up to 6 wt% sucrose; 25 to 150 mM NaCl; 1 to about 30 mM sodium phosphate; wherein the composition has a pH of 6.0 to pH 7.0.

11. The stabilized composition of claim 6 wherein the further stabilizing ingredient is calcium chloride, and the composition comprises 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; up to 5 mM calcium chloride; optionally 0.5 to 6 wt% sucrose or trehalose; optionally 0 to100 mM NaCl; optionally up to 10 mM xylitol; 1 to 30 mM sodium phosphate; wherein the composition has a pH of 6.0 to pH 7.0.

12. The stabilized composition of claim 6 wherein said further stabilizing ingredient is xylitol and the composition comprises 25 to 75 mg/ml of etanercept; 1-10 wt.% xylitol; 1 to 30 mM sodium phosphate; optionally up to 5 wt% meglumine; optionally up to 5 mM NaCl; and optionally up to 5 wt% sucrose; and having a pH of 6.0 to 6.6.

13. The stabilized composition of claim 6 wherein said further stabilizing ingredient is sodium chloride, and wherein the composition comprises 25 to 75 mg/ml etanercept, 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; about 150 mM of sodium chloride, 1 to 30 mM sodium phosphate; and 0 to 5 wt% sucrose or trehalose or combination thereof; wherein the composition has a pH of 6.0 to pH 7.0.

14. The stabilized composition of claim 6 wherein said further stabilizing ingredient is meglumine and wherein the composition comprises: 25 to 75 mg/ml etanercept, 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 1-30 mM of sodium phosphate; up to 10% meglumine; optionally up to 5 wt% sucrose; and optionally up to 100 mM sodium chloride, wherein the composition has a pH of 6.0 to 7.0.

15. The stabilized composition of claim 6 wherein the composition is characterized by:

(a) an SEC analysis at T_4 of greater than 90, 91, 92, 93, 94, 95, 96, or 97 wt% monomer content; and less than 3, 2 or 1 wt% aggregate(s) content; and

(b) an HIC analysis at T_2 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 4, 3, 2 or 1 wt%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater

than 80, 81, 82, 83, 84 or 85 wt%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20, 19, 18, 17, 16, 15, 14, or 13 wt%; and

(c) an HIC analysis at T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 3, 2 or 1 wt%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80, 81, 82, 83, 84 or 85 wt%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20, 19, 18, 17, 16, 15, 14 or 13 wt%.

16. A method for reducing the number of sub-visible particles in an etanercept formulation, said method comprising the step of adding surfactant selected from polysorbate or poloxamer surfactants to an etanercept formulation in an amount constituting .0001 to 0.5 w/v % of the formulation such that the number of subvisible particles per ml of the formulation having a size of 1 to 10 microns are reduced by at least 50%, and preferably by at least about 70%, in comparison to the same formulation prepared in the absence of said surfactant; where the number of sub-visible particles is measured by flowcam analysis conducted at the time the formulation is prepared and prior to any appreciable storage or thermal stress thereof.

17. The method of claim 16, wherein the etanercept formulation is free or essentially free of arginine.

18. The method of claim 17 wherein the surfactant is polyosrbate 80.

19. An article of manufacture comprising containment means such as a vial or injection device containing an etanercept formulation in final dosage form, said formulation comprising etanercept and a pharmaceutically acceptable surfactant selected from polysorbate and poloxamer surfactants, and wherein the amount of sub-visible particles present in the contained formulation is substantially reduced in comparison to the same formulation lacking the surfactant.

20. The article of claim 19 wherein the etanercept formulation is free or essentially free of arginine.

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition stabilized for long term storage comprising etanercept and a stabilizer for preventing, inhibiting or reducing the occurrence of subvisible particles in the composition, wherein the stabilizer comprises a surfactant selected from the group consisting of polysorbate surfactants and poloxamer surfactants, and capable of affording a significant reduction in sub-visible particles in the composition in comparison to an etanercept composition containing no surfactant; a buffer; optionally a sugar; optionally a salt; wherein the composition has a pH of between about 6 and about 7, wherein the composition is free of arginine as a stabilizer, and
   wherein a number of sub-visible particles per ml of the formulation having size of 1-10μm is at least about 50% lower than in the same composition having no polysorbate surfactant .

2. The stabilized composition of claim 1 wherein the stabilizer comprises a polysorbate surfactant selected from the group consisting of polysorbate 80, polysorbate 60, poysorbate 40 and polysorbate 20.

3. The stabilized composition of claim 2 wherein the stabilizer comprises polysorbate 80.

4. The stabilized composition of claim 1 wherein the stabilizer comprises a poloxamer surfactant, and the poloxamer surfactat is Pluronic F-68.

5. The stabilized composition of claim 1 wherein the composition has (i) less than 2500 particles/ml having a size of 5-10μm; (ii) less than 3500 particles having size of about 2-5μm and (iii) less than 700 particles/ml having size of about 1-2 μm.

6. The stabilized composition of claim 1 wherein the composition comprises 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; 1 mM to 20 mM magnesium chloride; optionally up to 6 wt% sucrose; 25 to 150 mM NaCl; and 1 to about 30 mM sodium phosphate.

7. The stabilized composition of claim 1 wherein the composition comprises 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 25 to 50 mg/ml of etanercept; up to 5 mM calcium chloride; optionally 0.5 to 6 wt% sucrose or trehalose; optionally 0 to100 mM NaCl; optionally up to 10 mM xylitol; and 1 to 30 mM sodium phosphate.

8. The stabilized composition of claim 1 wherein the composition comprises 25 to 75 mg/ml etanercept, 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; about 150 mM of sodium chloride, 1 to 30 mM sodium phosphate; and 0 to 5 wt% sucrose or trehalose or combination thereof.

9. The stabilized composition of claim 1 wherein the composition comprises: 25 to 75 mg/ml etanercept, 0.01 to 0.05 %w/v of the polysorbate or poloxamer surfactant; 1-30 mM of sodium phosphate; up to 10% meglumine; optionally up to 5 wt% sucrose; and optionally up to 100 mM sodium chloride.

10. The stabilized composition of claim 1 wherein the composition is characterized by:

(a) an SEC analysis at T_4 of greater than 90wt% monomer content; and less than 3 wt% aggregate(s) content; and

(b) an HIC analysis at T_2 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 4 wt%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt%; and

(c) an HIC analysis at T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 3 wt%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt%.

11. A method for reducing the number of sub-visible particles in an etanercept formulation, said method comprising the step of adding surfactant selected

from polysorbate or poloxamer surfactants to an etanercept formulation in an amount constituting 0.0001 to 0.5 w/v% of the formulation such that the number of subvisible particles per ml of the formulation having a size of 1 to 10 microns are reduced by at least 50%, and preferably by at least about 70%, in comparison to the same formulation prepared in the absence of said surfactant; where the number of sub-visible particles is measured by flowcam analysis conducted at the time the formulation is prepared and prior to any appreciable storage or thermal stress thereof, and wherein the formulation is free of arginine.

12. The method of claim 11 wherein the surfactant is polysorbate 80.

13. An article of manufacture comprising containment means such as a vial or injection device containing an etanercept formulation in final dosage form, said formulation comprising etanercept and a pharmaceutically acceptable surfactant selected from polysorbate and poloxamer surfactants, and wherein the amount of sub-visible particles present in the contained formulation is substantially reduced in comparison to the same formulation lacking the surfactant, and wherein the formulation is free of arginine.