CLAIMS

1 A biphasic pharmaceutical formulation comprising:

at least 25 mg/mL of polyethylene glycol (PEG);

at least 100 mg/mL of a VEGF antagonist protein, wherein less than 50% of the VEGF antagonist protein is present in a liquid phase with PEG, and the remainder of the VEGF antagonist protein is present in a solid phase in equilibrium with the liquid phase, wherein the solid phase is excluded from the liquid phase by PEG, and

a semi-permeable membrane, wherein the semi-permeable membrane surrounds the liquid phase and preferentially retains PEG while allowing diffusion of the VEGF antagonist protein through the membrane,

wherein the VEGF antagonist protein at least 80% native conformation, structure or function for at least 30 days at physiological temperature, and the liquid phase has access to an environment with a lower concentration of the VEGF antagonist protein through the semi-permeable membrane.

2. The biphasic pharmaceutical formulation of claim 1, wherein said VEGF antagonist protein is aflibercept and is between 100 mg/mL and 1400 mg/mL.

3. The biphasic pharmaceutical formulation of claim 1 or 2, wherein the concentration of PEG is between 25 mg/mL and 150 mg/mL.

4. The biphasic pharmaceutical formulation of claim 1 or 2, wherein the concentration of the VEGF antagonist protein is between 100 mg/mL and 500 mg/mL.

5. The biphasic pharmaceutical formulation of claim 1 or 2, wherein said solid phase comprises between 0.05 mg/mL and 50 mg/mL of said VEGF antagonist protein.

6. The biphasic pharmaceutical formulation of claim 1 or 2, wherein said VEGF antagonist protein has a molecular weight of 25 kD to 160 kD.

7. The biphasic pharmaceutical composition of claim 1 or 2, wherein said VEGF antagonist protein is a receptor-Fc-fusion protein.

8. The biphasic pharmaceutical formulation of claim 1 or 2, wherein said VEGF antagonist protein in the solid phase is stable for at least 60 days at physiological temperature.

9. The biphasic pharmaceutical formulation of claim 1 or 2, wherein at least 85% of said VEGF antagonist protein in the solid phase has a native molecular weight at 60 days at physiological temperature as determined by size-exclusion chromatography.

10. The biphasic pharmaceutical formulation of claim 1 or 2, wherein said protein in the solid phase is more stable than an equivalent concentration of the solid phase without PEG or in a closed biphasic system.

11. The biphasic pharmaceutical formulation of claim 1, wherein said environment is a physiological environment.

12. A biphasic pharmaceutical formulation, wherein said biphasic pharmaceutical formulation comprises:

a. polyethylene glycol (PEG) at a concentration that limits protein solubility to less than 50 mg/ml and greater than 0.5 mg/ml;

b. at least 100 – 1400 mg/mL of said VEGF antagonist protein, wherein less than 70% of the VEGF antagonist protein is present in a liquid phase with PEG, and the remainder of the VEGF antagonist protein is present in a solid phase in equilibrium with the liquid phase; and,

c. a semi-permeable membrane surrounding the liquid phase,

wherein said VEGF antagonist protein has at least 80% native conformation, structure or function upon release from said biphasic formulation for at least 30 days at physiological temperature, and said soluble VEGF antagonist protein can diffuse through the semi-permeable membrane and the PEG is preferentially retained within the membrane.

13. The formulation of claim 12, wherein said PEG is fully soluble, is only in the liquid phase, and is at a lower concentration in said liquid phase than said VEGF antagonist protein in said solid phase and wherein the VEGF antagonist protein is aflibercept.

14. A biphasic pharmaceutical formulation for use in the treatment of a patient in need thereof, wherein said biphasic pharmaceutical formulation comprises:

a. at least 25 mg/mL of polyethylene glycol (PEG);

b. at least 100 mg/mL of aflibercept, wherein less than 50 mg/mL of the aflibercept is present in a liquid phase with PEG, and the remainder of the aflibercept is present in a solid phase in equilibrium with the liquid phase and;

c. a semi-permeable membrane, wherein the semi-permeable membrane surrounds the liquid phase and preferentially retains PEG while allowing diffusion of the aflibercept through the membrane, and

wherein said aflibercept has at least 80% native conformation, structure or function for at least 30 days at physiological temperature, and has access through a porous structure to an environment in said patient with a lower concentration of said protein.