Claims:

1. A method of producing etanercept from Chinese hamster ovary cells (CHO), the method comprising running an N-1 bioreactor system using a recirculating tangential flow filtration (RTF) or an alternating tangential flow filtration (ATF) cell retention device under conditions that maintain a cell aggregate size of at least 20 µm.

2. The method of claim 1, wherein the method is performed under conditions that maintain a cell aggregate size of no more than 200 µm.

3. The method of claim 1, wherein the method is performed under conditions that maintain a cell aggregate size of between 20 µm and 150 µm.

4. The method of claim 3, wherein the method is performed under conditions that maintain a cell aggregate size of between 20 µm and 95 µm.

5. The method of any one of claims 1-4, wherein the system utilizes a tubing length, tubing cross-sectional area, and flow rate which provides an η of 20 µm using Formula 1:

$$\eta = \left(\frac{\nu^3}{\epsilon}\right)^{\frac{1}{4}}$$

wherein ϵ is [U^3/L], L is the length of tubing connecting the bioreactor and a RTF or ATF cell retention device, U is [flow rate in tubing/cross-sectional area of tubing], and ν is [cell culture viscosity/cell culture density].

6. The method of claim 5, wherein η is no greater than 200 µm using Formula 1.

7. The method of claim 5 or claim 6, wherein the flow rate is selected from (i) about 4 mL/min/fiber to about 16 mL/min/fiber for a hollow fiber module, (ii) about 360 L/m^2/hr to about 720 L/m^2/hr for flat sheet filter modules, and (iii) about 1 L/m/channel to about 4 L/m/channel for stacked plate modules; the cell culture viscosity is selected from about 1 to about 6 centipoise; and the cell culture density is selected from about 1 g/L to about 1.5 g/L.

8. A formulation comprising etanercept produced using the method of any one of claims 1-7.

9. The formulation of claim 8, wherein said formulation consists of 50 mg/mL of etanercept, 1% sucrose (w/v), 100 mM sodium chloride, 25 mM sodium phosphate, 25 mM L-arginine, and water.

10. The formulation of claim 8, wherein said formulation consists of 25 mg of etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine in a lyophilized powder.

11. The formulation of claim 8, wherein said formulation consists of 50 mg/mL of etanercept, 1% sucrose (w/v), 120 mM sodium chloride, 25 mL L-arginine, and water.

12. The formulation of claim 10, wherein said lyophilized powder is in a multiple-use vial.

13. The formulation of claim 9 or claim 11, wherein 1 mL of said formulation is in a prefilled syringe or SURECLICK® autoinjector.

14. The formulation of claim 9 or claim 12, wherein 0.51 mL of said formulation is in a prefilled syringe or SURECLICK® autoinjector.

15. Etanercept produced using the method of any one of claims 1-7 for use in therapy.

16. Use of etanercept produced using the method of any one of claims 1-7 in the manufacture of a medicament for treating rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis.

17. A kit comprising the formulation of any one of claims 8-14 and instructions for use of said formulation.