material to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability during the freeze-drying process and/or to improve stability of the lyophilized product upon storage. Pikal, M. (1990), Biopharm. 3(9)26-30 and Arakawa et al. (1991), Pharm. Res. 8(3):285-291.

[0005] A designed molecule with specific biological targets and the resulting dosage requirements for product poses new problems for the manufacturing process. The current art involves a simple process where product is formulated to a targeted concentration and then filled into containers at a set volume.

SUMMARY

[0006] This disclosure is directed to a process to generate lyophilized drug product. In particular, it relates to the formulation, fill, and assurance of the required amount of product present post-reconstitution with a fixed volume of diluent of a lyophilized product for use.

[0006a] In one aspect, the present disclosure provides a process for making a lyophilized pharmaceutical formulation comprising a therapeutic protein, which comprises: a. providing a formulation comprising a bulk amount of the therapeutic protein, b. measuring the concentration of the therapeutic protein in the bulk formulation, c. dispensing a fill weight of the bulk formulation according to the following formula into a container to achieve a target fixed dose of the protein in the container, and d. lyophilizing the formulation in the container;

$$\text{fill weight} = \frac{(\text{target fixed dose of the therapeutic protein}) \times (\text{density of the bulk formulation})}{\text{therapeutic protein concentration in bulk formulation.}}$$

[0007] Provided in accordance with the present disclosure is a process for making a lyophilized pharmaceutical formulation of a therapeutic protein, which comprises:

(a) providing a formulation of a bulk amount of the therapeutic protein,

(b) measuring the concentration of the therapeutic protein in said bulk formulation,

(c) adjusting the fill weight of the protein in said bulk formulation to achieve a fixed dose of the protein, and

CLAIMS

What is claimed is:

1. A process for making a lyophilized pharmaceutical formulation comprising a therapeutic protein, which comprises:
    a. providing a formulation comprising a bulk amount of the therapeutic protein,
    b. measuring the concentration of the therapeutic protein in the bulk formulation,
    c. dispensing a fill weight of the bulk formulation according to the following formula into a container to achieve a target fixed dose of the protein in the container, and
    d. lyophilizing the formulation in the container;

$$\text{fill weight} = \frac{(\text{target fixed dose of the therapeutic protein}) \times (\text{density of the bulk formulation})}{\text{therapeutic protein concentration in bulk formulation.}}$$

2. The process of claim 1, wherein the process further comprises reconstituting the lyophilized formulation, wherein the concentration of the therapeutic protein in the reconstituted formulation is less than or equal to about 20 mg/mL.
3. The process of claim 1, wherein the therapeutic protein is selected from romiplostim, blinatumomab, infliximab, trastuzumab, AMG 701, and AMG 330.
4. The process of claim 2, wherein the therapeutic protein is romiplostim and the concentration of romiplostim in the reconstituted formulation is about 0.5 mg/mL.
5. The process of claim 2, wherein the reconstituted formulation comprises about 0.5 mg/mL romiplostim, about 10 mM histidine, about 4% w/v mannitol, about 2% w/v sucrose and about 0.004% polysorbate 20, has a pH of about pH 5.0.
6. The process of claim 2, wherein the therapeutic protein is blinatumomab and the concentration of blinatumomab in the reconstituted formulation is about 55 μg/mL.
7. The process of claim 2, wherein the reconstituted formulation comprises about 55 μg /mL blinatumomab, about 25 mM citric acid monohydrate, about 15% (w/v) trehalose, about 200 mM L-lysine hydrochloride, and about 0.1% (w/v) polysorbate 80, and has a pH of about pH 7.0.
8. The process of claim 2, wherein the therapeutic protein is infliximab and the concentration of infliximab in the reconstituted formulation is 20 ± 1.5 mg/mL.

9. The process of claim 2, wherein the reconstituted formulation comprises about 20 ± 1.5 mg/mL infliximab, about 10 mM sodium phosphate, about 10% (w/v) sucrose, and about 0.01% (w/v) polysorbate 80, and has a pH of about pH 7.2.
10. The process of claim 2, wherein the therapeutic protein is trastuzumab and the concentration of trastuzumab in the reconstituted formulation is about 21 mg/mL.
11. The process of claim 2, wherein the reconstituted formulation comprises about 21 mg/mL trastuzumab, about 0.303 mg/mL L-histidine, about 0.470 mg/mL L-histidine hydrochloride monohydrate, about 19.1 mg/mL á,á-trehalose dihydrate, and about 0.0840 mg/mL polysorbate 20, and has a pH of about pH 6.1.
12. The process of claim 2, wherein the therapeutic protein is AMG 701 and the concentration AMG 701 in the reconstituted formulation is about 1 mg/mL.
13. The process of claim 2, wherein the reconstituted formulation comprises about 1 mg/mL AMG 701, about 10 mM L-glutamic acid, about 9.0% (w/v) sucrose, and about 0.010% (w/v) polysorbate 80, and has a pH of about pH 4.2.
14. The process of claim 2, wherein the therapeutic protein is AMG 330 and the concentration of AMG 330 in the reconstituted formulation is about 0.5 mg/mL.
15. The process of claim 2, wherein the reconstituted formulation comprises about 0.5 mg/mL AMG 330, about 10 mM potassium phosphate, about 8.0% (w/v) sucrose, about 1.0% (w/v) sulfobutylether betacyclodextrin (SBE-CD), and about 0.010% (w/v) polysorbate 80, and has a pH of about pH 6.1.
16. The process of claim 1, wherein the protein concentration of the therapeutic protein in the bulk formulation is less than or equal to about 25 mg/mL.
17. The process of claim 1, wherein the therapeutic protein is a bispecific single chain antibody construct.
18. The process of claim 1, wherein the therapeutic protein is selected from AMG 701 and AMG 330.
19. The process of claim 2, wherein the reconstituting comprises using water for injection.
20. The process of claim 2, wherein the reconstituted formulation is suitable for subcutaneous administration.
21. The process of claim 2, wherein the reconstituted formulation is suitable for intravenous administration.