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 invention 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.

[0007] Disclosed herein 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
- **(d)** lyophilizing the protein fill weight-adjusted formulation to achieve a final formulation in a container.

wherein the product concentration post reconstitution with a fixed volume is within a predetermined acceptance range. In one aspect, the present invention is directed to 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 d. lyophilizing the protein fill weight-adjusted formulation to achieve a final formulation in a container wherein the product concentration post reconstitution with a fixed volume is within a predetermined acceptance range; wherein the adjusted fill weight of the protein is calculated according to the formula

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

[0008] In the foregoing process, the protein concentration in the final formulation is preferred to be less than or equal to about 20 or 25 mg/mL, with about 0.5 mg/mL, about 0.05 mg/mL about 18 mg/mL about 20 mg/mL and about 21 mg/mL most preferred. Preferred therapeutic proteins in the processes of disclosed herein are romiplostim, blinatumomab, infliximab, trastuzumab, AMG 701, and AMG 330. AMG 701 and AMG 330 are bispecific single chain antibody constructs and other bispecific single chain antibody constructs (e.g., bispecific T cell engagers) are preferred therapeutic proteins in the processes disclosed herein. Preferred pharmaceutical excipients present in the formulation comprise sugars, with trehalose, sucrose and a hydrate of either most preferred. Preferred pharmaceutical excipients also comprise buffers, with histidine, citric acid monohydrate, sodium phosphate, potassium phosphate, and glutamic acid preferred. Preferred excipients further comprise surfactants, with polysorbate 20 and polysorbate 80 most preferred. Preferred excipients and therapeutic proteins used in accordance with the processes disclosed herein appear in Table 1, with about the preferred concentrations of each listed below each protein and excipient.

[0009] **Table 1—Preferred Formulation Components**

Protein	**Sugar**	**Buffer**	**Bulking agent/Solubilizing agent**	**Surfactant**	**pH**
romiplostim 0.5 mg/mL	Sucrose 2% w/v	Histidine 10 mM	Mannitol 4% w/v	Polysorbate 20 0.004% w/v	5.0
blinatumomab 55 mcg/mL	Trehalose 15% w/v	Citric acid monohydrate 25 mM; L-lysine hydrochloride 200 mM	--	Polysorbate 80 0.1% w/v	7.0
infliximab 20 ± 1.5 mg/mL	Sucrose 10% w/v	Sodium phosphate 10 mM	--	Polysorbate 80 0.01% w/v	7.2

trastuzumab 21 mg/mL	á,á-trehalose dehydrate 19.1 mg/mL	Histidine 0.303 mg/mL; L-histidine hydrochloride monohydrate 0.470 mg/mL	--	Polysorbate 20 0.0840 mg/mL	6.1
AMG 701 1 mg/mL	Sucrose 9% w/v	L-Glutamic acid 10 mM	--	Polysorbate 80 0.010% w/v	4.2
AMG 330 0.5 mg/mL	Sucrose 8% w/v	Potassium phosphate 10 mM	SBE-CD 1% w/v	Polysorbate 80 0.010% w/v	6.1

[0010] Further in accordance with the disclosure, the formulation may comprise other excipients as described hereinbelow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 is a response surface map showing an example design space for a low dose product in which formulation and fill weight would follow a typical control strategy. The gray space represents wherein method/reconstitution variability would have a greater than 50% probability of having a failed protein concentration result. The large square shows the current operating range for formulation development. The smaller rectangle shows an effective operating range.

[0012] Figure 2 is a response surface map showing an example design space for a low dose product in which osmolality is considered in addition to bulk concentration and fill volume. The light gray region shows the stepped-in drug product concentration specification wherein method/reconstitution variability would have a greater than 50% probability of having a failed protein concentration result. The dark gray area shows the osmolality specification. The rectangle shows the design space range for the fill weight (x-axis) and the formulated bulk concentration (y-axis) in-process control (IPC)/alert limit operational range (ALOR).

[0013] Figure 3 is a response surface map showing an example of a viable but not fault-tolerant fill weight and formulation control strategy. The curve and two-headed arrow show the likely fill target error. The light gray area represents the stepped-in drug product concentration

specification, with the light gray area showing where method/reconstitution variability would have a greater than 50% probability of having a failed protein concentration result. The dark gray area defines the osmolality specification. The rectangle shows the IPC/ALOR.

[0014] Figure 4 is a response surface map showing an example of a fill weight and formulation control strategy with difficulty at the edge of range control, with an expected lower formulated bulk and lower fill weight. The left curve and two-headed arrow shows the likely fill target error at a low fill volume. The right curve and two-headed arrow show the likely fill target error at a higher fill volume. The light gray area represents the stepped-in drug product concentration specification, with the light gray area showing where method/reconstitution variability would have a greater than 50% probability of having a failed protein concentration result. The dark gray area defines the osmolality specification. The rectangle shows the IPC/ALOR.

CLAIMS

What is claimed is:

1. 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
    d. lyophilizing the protein fill weight-adjusted formulation to achieve a final formulation in a container;

    wherein the product concentration post reconstitution with a fixed volume is within a predetermined acceptance range;

    wherein the adjusted fill weight of the protein is calculated according to the formula

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

2. The process of claim 1, wherein the protein concentration in the final 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 1, wherein the therapeutic protein is romiplostim and the therapeutic protein concentration in the final formulation is about 0.5 mg/mL.
5. The process of claim 1, wherein the final formulation comprises about 0.5 mg/mL romiplostim in about 10 mM histidine, about 4% w/v mannitol, about 2% w/v sucrose and about 0.004% polysorbate 20 at about pH 5.0.
6. The process of claim 1, wherein the therapeutic protein is blinatumomab and the therapeutic protein concentration in the final formulation is about 55 μg/mL.
7. The process of claim 1, wherein the formulation comprises about 55 μg /mL blinatumomab in 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 at about pH 7.0.
8. The process of claim 1, wherein the therapeutic protein is infliximab and the therapeutic protein concentration in the final formulation is 20 ± 1.5 mg/mL.

9. The process of claim 1, wherein the final 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 at about pH 7.2.
10. The process of claim 1, wherein the therapeutic protein is trastuzumab and the therapeutic protein concentration in the final formulation is about 21 mg/mL.
11. The process of claim 1, wherein the final 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 at about pH 6.1.
12. The process of claim 1, wherein the therapeutic protein is AMG 701 and the therapeutic protein concentration in the final formulation is about 1 mg/mL.
13. The process of claim 1, wherein the final 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 at about pH 4.2.;
14. The process of claim 1, wherein the therapeutic protein is AMG 330 and the therapeutic protein concentration in the final formulation is about 0.5 mg/mL.
15. The process of claim 1, wherein the final 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 at about pH 6.1.
16. The process of claim 1, wherein the protein concentration in the final 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.