

METHOD OF OPTIMIZING A FILLING RECIPE FOR A DRUG CONTAINER**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of the filing date of U.S. Provisional Patent Application No. 63/191,797, filed May 21, 2021, which is hereby incorporated by reference in its entirety.

FIELD OF DISCLOSURE

[0002] The present disclosure generally relates to filling recipes for drug containers and, more particularly, to a universal method of optimizing a filling recipe for a drug container.

BACKGROUND

[0003] Existing filling recipes for filling drug containers, such as recipes for loading mAb formulation in a nested syringe and vial line, are known. However, many existing filling recipes create several problems, including extended fill weight optimization cycles, substantial rejected units, and a lower manufacturing yield. In addition, existing filling recipes often have low process capability demonstrated by a poor process capability index, e.g., Cpk, <1.33 value.

[0004] More specifically, existing fill recipes are individually tailored to a single drug product, each of which has a unique filling process and set of operating parameters. As a result, a pump in a manufacturing facility carrying out the filling recipe must be calibrated each time a new filling recipe is needed for a new drug product. In addition, the time involved to calibrate the pump or related equipment in a manufacturing facility before beginning the filling process according to a particular filling recipe is often lengthy. For example, there are typically many cycles needed, such as multiple number of strokes of the pump, until the pump is able to operate according to a particular filling recipe. This increases the overall time to fill a drug container, such as a syringe or a vial, using a specific filling recipe for a drug product, leading to inefficiencies in the manufacturing and filling processes. In addition, existing filling recipes typically migrate out of a desired range of a fill volume of the container, causing problems in the manufacturing system and process. In one example, when the fill volume is outside of the desired fill volume range, the unit is discarded, and the pump must be retaught how to fill the target within the range, again leading to inefficiencies in the manufacturing process.

SUMMARY

[0005] In accordance with a first aspect, a method of filling a vial comprises providing a pump corresponding to a vial, and setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees. The method further comprises setting a no adjustment limit for a fill weight of the vial to T1, with T1 being at or in a range of about 2% more or less than a fill weight of a target fill weight T0, and wherein a process performance index Cpk (Cpk) for the vial throughout a fill cycle exceeds a minimum value.

[0006] In accordance with a second aspect, a method of filling a plurality of vials of a nested syringe and vial line comprises providing a plurality of pumps corresponding to a plurality of vials of a nested syringe and vial line, and setting a drip retraction parameter for each pump in the plurality of pumps to any value equal to or less than 20 degrees. The method also includes filling each vial of the plurality of vials with a drug product via a corresponding pump of the plurality of pumps; and wherein a Cpk for each vial of the plurality of vials exceeds a minimum value throughout a fill cycle.

[0007] In accordance with yet another aspect, a method of optimizing a filling recipe for a nested syringe and vial line comprises setting a drip retraction parameter for at least one pump in an offline manufacturing system corresponding to any value equal to or less than 20 degrees, and monitoring a performance of the at least one pump with the drip retraction parameter

of the at least one pump set to any value equal to or less than 20 degrees. The method also includes obtaining at least a minimum value for a Cpk for the at least one container throughout at least one fill cycle and for at least one drug product using the at least one pump in the offline manufacturing system; and finalizing a filling recipe for a nested syringe and vial line using data from fill cycles of the at least one drug product using the at least one pump in the offline manufacturing system.

[0008] In accordance with yet another aspect, a method of filling a vial may comprise providing a pump corresponding to a vial, setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees, and setting a no adjustment limit for a fill weight of the vial to any value within a range of a target fill weight T0 and T1, with T1 being at or in a range between the target fill weight T0 and T2. So configured, a minimum value for a process performance index Cpk (Cpk) for the vial throughout a fill cycle is exceeded.

[0009] In some aspects, setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees may comprise setting the drip retraction parameter for the pump to one of 10 degrees, 20 degrees, or any value in a range of 10 degrees to 20 degrees. In addition, the method may further comprise setting an end drip retraction value to 290 degrees when setting the drip retraction parameter to 20 degrees or setting an end drip retraction value to 280 degrees when setting the drip retraction parameter to 10 degrees. In addition, providing a pump corresponding to a vial may comprise providing a pump corresponding to a vial of a nested syringe and vial line.

[0010] In other aspects, providing a pump corresponding to a vial may comprise providing one or more of a first fill set or a second fill set, the first fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 2.0mm, and the second fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 3.0mm.

[0011] In still other aspects, wherein a Cpk for the vial exceeds a minimum value throughout a fill cycle may comprise one or more of: (1) the Cpk for the vial exceeds a value of 1.33; or (2) the Cpk for the vial exceeds the minimum value during a temperature range throughout the fill cycle, the temperature range is one of: (1) 5 (+/-3) degrees Celsius; (2) 20 (+/-5) degrees Celsius; or (3) 10 to 19 degrees Celsius.

[0012] In other aspects, the method may further comprise filling the vial with a drug product via the pump, wherein the drug product has one or more of the following characteristics: (a) a density in a range of about 1.0-1.2 g/cm³; (b) a viscosity in a range of about 1.0-10.0 cP; and (c) a surface tension in a range of about 40.0-72.7 mN/m. In one example, the drug product has a density in a range of 1.0-1.2 g/cm³; a viscosity in a range of about 1.0-10.0 cP; and a surface tension in a range of about 40.0-72.7 mN/m. In another example, the drug product comprises a biologic drug (e.g., peptides, mAb, siRNA) or a small molecule drug.

[0013] In still other aspects, the method may further comprise monitoring a performance of the filling recipe in the nested syringe and vial line and obtaining at least a minimum value for the Cpk for the at least one container for each pump in a plurality of pumps in the nested syringe and vial line.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] It is believed that the disclosure will be more fully understood from the following description taken in conjunction with the accompanying drawings. Some of the drawings may have been simplified by the omission of selected elements for the purpose of more clearly showing other elements. Such omissions of elements in some drawings are not necessarily indicative of the presence or absence of particular elements in any of the example embodiments, except as may be explicitly delineated in the corresponding written description. Also, none of the drawings is necessarily to scale.

[0015] FIG. 1 is a schematic representation of one embodiment of an offline filling system utilizing a filling recipe of the present disclosure;

- [0016] FIG. 2A is a perspective view of a filler of the system of FIG. 1;
- [0017] FIG. 2B is a portion of the filler of FIG. 2A;
- [0018] FIG. 2C is a perspective view of a fill set of the system of FIG. 1;
- [0019] FIG. 2D is a perspective view of another fill set of the system of FIG. 1;
- [0020] FIG. 2E is a perspective view of an exemplary fill target of the system of FIG. 1;
- [0021] FIG. 3A is a chart depicting parameters of each of the fill sets of FIG. 1;
- [0022] FIG. 3B is a chart depicting in process control parameters of the fill sets of FIG. 1;
- [0023] FIG. 3C is a chart depicting product characteristics of drug products for use with the methods of the present disclosure;
- [0024] FIG. 4 is a flow chart depicting a filling recipe parameter optimization strategy relative to the filling recipe of the present disclosure;
- [0025] FIG. 5A is a perspective view of fill performance results of a vial after filling at various drip retraction values;
- [0026] FIG. 5B is a chart depicting aspects of an exemplary fill recipe used with the fill performance results of FIG. 5A;
- [0027] FIG. 6A depicts an exemplary filling recipe according to one aspect of the present disclosure;
- [0028] FIG. 6B is a graph depicting filling performance results of the filling recipe of FIG. 6A;
- [0029] FIG. 6C is a chart depicting the filling performance results of the graph of FIG. 6B;
- [0030] FIG. 7A is a chart depicting needle parameters of a needle used with a filling recipe of the present disclosure;
- [0031] FIG. 7B is a chart depicting pump parameters of at least one pump used with a filling recipe of the present disclosure;
- [0032] FIG. 8A is a graph depicting filling performance results of the filling recipe of the present disclosure in a temperature range of 10 – 11 degrees Celsius and using a second fill set of the system of FIG. 1;
- [0033] FIG. 8B is a chart depicting the filling performance results of the graph of FIG. 8A;
- [0034] FIG. 9A is a graph depicting the filling performance results of the filling recipe of the present disclosure at a temperature of about 19 degrees Celsius and using the second fill set of the system of FIG. 1;
- [0035] FIG. 9B is a chart depicting the filling performance results of the graph of FIG. 9A;
- [0036] FIG. 10A is a graph depicting the filling performance results of the filling recipe of the present disclosure at a temperature of about 10-11 degrees Celsius and using the first fill set of the system of FIG. 1;
- [0037] FIG. 10B is a chart depicting the filling performance results of the graph of FIG. 10A;
- [0038] FIG. 11A is a graph depicting the filling performance results of the filling recipe of the present disclosure at a temperature of about 19 degrees Celsius and using the first fill set of the system of FIG. 1;
- [0039] FIG. 11B is a chart depicting the filling performance results of the graph of FIG. 11A;
- [0040] FIG. 12 is a schematic representation of a manufacturing line in a manufacturing plant using the optimized filling recipe of the present disclosure;
- [0041] FIG. 13A is a perspective view of a nested syringe and vial line of the manufacturing line of FIG. 12;

- [0042] FIG. 13B is a schematic view of the nested syringe and vial line of FIG. 13A;
- [0043] FIG. 13C is a perspective view of a plurality of pumps corresponding to a plurality of vials of the nested syringe and vial line of FIGS. 13A-13B;
- [0044] FIG. 14 is a chart depicting filling performance results of the filling recipe of the present disclosure in at least one of the nested syringe and vial line of FIG. 12; and
- [0045] FIG. 15 is a chart depicting filling performance results of a previously used filling recipe used in a nested syringe and vial line.

DETAILED DESCRIPTION

[0046] Generally, an efficient filling recipe for filling formulations comprising therapeutic proteins in a nested syringe and vial line is disclosed. The universal filling recipe include a drip retraction parameter optimization within a specified value, which results in a significantly more efficient fill recipe compared to other existing, known filling recipes. In particular, and for example, the new filling recipe of the present disclosure may be used with many different drug products and results in 95% reduction in fill weight optimization cycles. This led to an improvement of 10-30% increase utilization of a nested syringe and vial line fill time and potentially saving a significant number of units, such as vials, from rejection. In at least one example, the drug products referred to herein comprise therapeutic proteins, such as monoclonal antibodies, as explained more below.

[0047] More specifically, and referring now to FIG. 1, an offline manufacturing system 10 utilizing a filling recipe of the present disclosure is depicted. In one example, the offline manufacturing system 10 is a small scale bench set-up in a pilot facility, which made various tests related to the new filling recipe easier to assess and update based on test results for various attempted recipes, for example. The offline manufacturing system 10 includes a filler 12, a first fill set 14, and a second fill set 16. The first fill set 14 includes a corresponding first fill target 18, such as a vial, and the second fill set 16 likewise includes a corresponding second fill target 20, also such as a vial. In one example, the filler 12 is a Bausch+Strobel (B&S) scale-down filler in which recipe optimization, including many experiments, were conducted before arriving at the optimal, universal filling recipe of the present disclosure. While the specific B&S scale-down filler was used, it will be appreciated that various other fillers may also or alternatively be used. In addition, while each of the first and second fill targets 18, 20 are referred to as a vial in one example, it will be understood that the fill targets 18, 20 may alternatively and more generally be any other similar drug container and still fall within the scope of the present disclosure. As explained more below, the optimal filling recipe selected from the recipe optimization from the scale-down filler 12 and first and second fill sets 12, 16 is transferable to a manufacturing line, such as a nested syringe and vial line in FIGS. 13A and 13B.

[0048] Referring now to FIGS. 2A-2E, a perspective view of each of the filler 12, first and second fill sets 14, 16 and first and second fill targets 18, 20 of FIG. 1 is depicted. In FIG. 2A, the filler 12 is a Bausch+Strobel Filler, a bench scale down filler, and more generally a developmental filler to support clinical and commercial manufacturing, as explained more below. Exemplary containers that may be used with this filler include bulk ISO 2R, 6R, 20R, 3cc, 5cc, 10cc, 20cc vials, bulk 1mL glass and 1 mL plastic syringes, and bulk 5cc plastic cartridges. The filler 12 includes a dosing vessel 21, a pump 22, such as a peristaltic pump, and a product bag 23. FIG. 2B depicts a portion of the filler 12 of FIG. 2A. In particular, the pump 22 is depicted cooperating with a fill target, such as the first fill target 18 or the second fill target 20. In this example, the first and second fill targets 18, 20 are the same vial, but may also be any other container and still fall within the scope of the present disclosure.

[0049] Referring now to FIG. 2C, the first filling set 14 of FIG. 1 is depicted. The first filling set 14 is a peristaltic pump and includes a bag 27, tubing 28A, and a needle 29A. The tubing 28A is coupled to the bag 27 at one end and the fill target 18 at the other end, such that the fluid in the bag is able to be drawn into the tubing and to the fill target 18 by way of the needle 29A, for

example. In this example, the outer diameter of the needle 29A is 2.0mm, the inner diameter of the needle is 1.6mm, and the inner diameter of the pump tubing 28A is 1.6 mm. In addition, the tubing 28A branches into two tubing and converges again. The two tubing have the same inner diameter in this example. For example, the inner diameter of the tubing 28B is 1.6mm. In a similar manner, FIG. 2D depicts the second fill set 16 of FIG. 1. Like the first fill set 14, the second fill set 16 is a peristaltic pump and includes the bag 27, tubing 28B, and a needle 29B, which is different from the needle 29A of the first fill set 14. Specifically, the tubing 28B is again coupled to the bag 27 at one end and the second fill target 20 at the other end, such that fluid in the bag is able to be drawn through the tubing and into the second fill target 20 by way of the needle 29B. In this example, the tubing 28B again branches into two tubing and then converges again, but the two tubing have a different inner diameter. For example, the inner diameter of the tubing 28B is 1.6mm and 3.2 mm, respectively. In addition, the outer diameter of the needle 29B is 3.0mm, the inner diameter of the needle is 2.6mm, and the inner diameter of the pump tubing is 1.6 mm.

[0050] Referring now to FIG. 2E, an exemplary fill target is depicted. In particular, the exemplary fill target may include the first and second fill targets 18, 20 of FIG. 1, for example. In this example, the first and second fill targets 18, 20 include a 1.3 mL fill in ISO 2R vial. For this exemplary fill target, the target weight is 1.365 grams, T2+ is 0.05grams, which is 1.415 grams, and T2- is 0.05 grams, which is 1.315 grams. Also, T1+ is 0.03 grams, which is 1.395 grams, and T1- is 0.03 grams, which is 1.335 grams. Further, the net weight no adjustment limit + is 0.02 grams, which is 1.385 grams, and the net weight no adjustment limit – is 0.02 grams, which is 1.345 grams.

[0051] Referring now to FIG. 3A, a chart depicting exemplary parameters of the first and second fill sets 14, 16 of FIG. 1, for example, is depicted. As indicated in the chart, and in this example, the first fill set 14 is a peristaltic pump filling assembly having a needle with an outer diameter of 2.0mm and an inner diameter of 1.6mm. In addition, the peristaltic pump filling assembly includes tubing (in FIG. 2C) having an inner diameter of 1.6mm. The chart in FIG. 3A also includes information about the second fill set 16, which in this example also includes a peristaltic pump filling assembly having a needle with an outer diameter of 2.0mm and an inner diameter of 2.6mm. Like the first fill set 14, the second fill set 16 also includes tubing having an inner diameter of 1.6mm, and another tubing having an inner diameter of 3.2mm, as mentioned above.

[0052] Referring now to FIG. 3B, various in process control parameters were initially set on the second fill set 16. In particular, a no adjustment limit for a fill weight of the second fill target 20, such as the vial, was set to T1, with T1 being at or in a range of about 2% more or 2% less than a fill weight of a target fill weight T0. Specifically, and in one example provided in the chart in FIG. 3B, the target fill weight T0 includes a volume of 1.3 mL and a mass of 1.365 grams. In this example, the no adjustment limit was 80% of T1, which may be +/- 0.02 grams of T1 +/- 0.03 grams. Thus, the fill target mass of a vial in which no adjustment is needed is any value in the range of 1.345 grams to 1.385 grams in this example. In another example, the no adjustment limit for a fill weight of the vial, such as the second fill target 20, may be set to any value within a range of a target fill weight T0 and T1, with T1 being at or in a range between the target fill weight T0 and T2 based on process performance, for example. In some examples, T1 is set at 2%, but may be changed.

[0053] Referring now to FIG. 3C, a chart listing parameters of various drug products initially used in the optimization process is depicted. In particular, the filling recipe of the present disclosure includes filling a vial, such as the vials of the first and second filling targets 18, 20, with a drug product via a pump, and the drug product includes a mAb formulation. In this example, the mAb formulations used are drug product 1 (DP1) and drug product 1 (DP2). As provided in the chart, at 5 degrees Celsius the density of DP1 is 1.055 g/cm³ and the viscosity is 4.857. At 25 degrees Celsius, the density of DP1 is 1.05 g/cm³, the viscosity is 2.604 cP, and the surface tension is 41.63 mN/m. At 5 degrees Celsius the density of DP2 is 1.054 g/cm³ and the viscosity is 4.07 cP. In addition, at 25 degrees Celsius, the density of DP2 is 1.049 g/cm³, the viscosity is 2.19 cP, and the surface tension is 43.716 mN/m. Thus, in this example, the drug product used in the filling recipe is a mAb formulation including one or more of:

(1) a density in a range of either about 1.054-1.055 g/cm³ at 5 degrees Celsius or about 1.049-1.05 g/cm³ at 25 degrees Celsius; (2) a viscosity in a range of either about 4.07-4.857 cP at 5 degrees Celsius or about 2.19-2.604 cP at 25 degrees Celsius, and a surface tension in a range of about 41.00-43.80 mN/m at 25 degrees Celsius.

[0054] The method disclosed herein can be used to fill any liquid drug product, such as drug products comprising a biologic drug (e.g., peptides, mAbs, siRNAs) and a small molecule drug, provided the drug product has a specified physical parameter range. More specifically, and in one example, the drug product may include one or more of the following characteristics: (1) a density in a range of about 1.0-1.2 g/cm³; and/or (2) a viscosity in a range of about 1.0-10.0 cP; and/or (3) a surface tension in a range of about 40.0-72.7 mN/m. In one example, preferred ranges for the viscosity are one or more of 1.0-8.0 cP, 1.0-6.0 cP, 1.0-5.0 cP, and 1.0-4.0 cP. In another example, the drug product has a density in a range of 1.0-1.2 g/cm³; a viscosity in a range of about 1.0-10.0 cP; and a surface tension in a range of about 40.0-72.7 mN/m. In another example, the drug product has one or more of a density in a range of 1.0-1.2 g/cm³ and a viscosity in a range of about 1.0-10.0 cP, and any value for a surface tension. Said another way, in one example, the determining factors for the filling recipe are the density and the viscosity of the drug product, and the filling recipe may work with any surface tension. It will be understood that a drug product meeting any of these parameters may be used with the methods and filling recipe of the present disclosure.

[0055] For example, in one example, manufacturing data suggests that a drug product with a viscosity of about 8.0 cP or more worked well with a drip retraction value of 20 degrees. In addition, in another example, the preferred density of the drug product is about 1.0-1.1 g/cm³. It will be appreciated that many other values within the density, viscosity, and surface tension ranges provided above may be used for the drug products used with the methods and filling recipes of the present disclosure and fall within the scope of the present disclosure.

[0056] Referring now to FIG. 4, a flow chart depicting a fill parameter optimization strategy for the drug product DP1 is provided. Specifically, in step 30 an initial optimization based on an existing filling recipe, which is referred to as existing filling recipe No. 1, was conducted on the second fill set 16. Next, in step 32, with this initially optimized DP1 filling recipe for the second fill set 16, a range of drip retraction parameters ranging from 0 degrees to 45 degrees was tested. In step 34, another existing filling recipe, referred to as existing filling recipe No. 2, was started and a range of drip retraction parameters from 10 degrees to 20 degrees was tested. A hybrid of existing filling recipe No. 1 and existing filling recipe No. 2 was then developed in step 36 and various drip retraction parameters were also tested, including 5 degrees, 10 degrees and 20 degrees. In step 38, the hybrid recipe was finalized for the second fill set 16 with a drip retraction parameter set at 20 degrees. Lastly, in step 40, the same filling recipe was used for the first fill set 14 and drip retraction parameters were set at 10 degrees and 20 degrees. Based on the fill performance, a filling recipe for the first fill set 14 was finalized with a drip retraction parameter set at 20 degrees.

[0057] Referring now to FIG. 5A, fill performance results of the second fill target 20, such as the vial, of the second fill set 16 after utilizing a filling recipe with various drip retraction values is provided. In particular, a test was conducted and the fill performance of the vial monitored when the drip retraction parameter of the filling recipe for the pump was set to each of 0 degrees, 10 degrees, 20 degrees, 30 degrees, 40 degrees, and 45 degrees. As noted in FIG. 5A, an air gap AG in the fill target 20 or vial increased with increasing drip retraction parameter leading to an air liquid bilayer, explaining a likely reason for poor fill performance when a higher drip retraction parameter is set in the filling recipe. As noted in the chart of FIG. 5B, while the drip retraction parameter set was different for each of the vials provided, all of the other parameters for the filling recipe used in these experiments were the same. In particular, the start pump dosing was set at 40 degrees, the pump dosing start ramp was set at 90 degrees, the pump dosing stop ramp was set at 210 degrees, the end pump dosing was set at 260 degrees, the end drip retraction was set at 310 degrees, and the distance run per dose was 766 degrees.

[0058] Referring now to FIG. 6A, a filling recipe including many of the same constant parameters in the optimization cycles documented in part in FIG. 5B, for example, is depicted, but with the drip retraction parameter set at 20 degrees for the second fill set 16. In particular, in the filling recipe, the start pump dosing was set at 40 degrees, the pump dosing start ramp was set at 90 degrees, the pump dosing stop ramp was set at 210 degrees, the end pump dosing was set at 260 degrees, the end drip retraction was set at 290 degrees, and the distance run per dose was 766 degrees.

[0059] Referring now to FIGS. 6B and 6C, the impact of the drip retraction parameter set at 20 degrees on fill performance of DP1 in the second fill set 16 is provided. Specifically, for 103 number of fills on the second fill set 16 using the filling recipe set forth in FIG. 6A, the minimum filling weight was 1.348 grams and the maximum filling weight was 1.384 grams, making the average fill weight 1.366 grams, with a standard deviation of 0.006. The process performance index Cpk value was 2.69, which is considerably higher than experiments using a filling recipe with the same parameters except for the drip retraction parameter of 45 degrees. Said another way, the process performance index was much higher when the drip retraction parameter was set to 20 degrees compared to higher values, such as 45 degrees, further indicating the impact of the drip retraction parameter on the fill performance.

[0060] Generally, the process performance index Cpk provides a value indicative of the efficiency of a particular process. In this example, the process performance index value Cpk relates to how close an actual fill weight of a container, such as a vial, is to a target fill weight. In addition, the process performance index value Cpk also relates to how close each subsequent fill rate of the additional containers, e.g., vials, are to each other. If there is a high number of the process performance index value Cpk, a given pump is providing an optimal performance. Likewise, a low number for the process performance index value Cpk indicates the pump is poorly performing. As it is important to fill a consistent dose of a drug product in each container (e.g., vial) during a manufacturing process, the higher the process performance index value Cpk, which is also indicative of the consistency of the filling process, is a critical value to the success of efficiently and accurately filling vials.

[0061] Referring now to FIGS. 7A and 7B, based on the optimization cycles and experimental data described above relative to a filling recipe for the exemplary drug product DP1 in the second fill set 16, a universal filling recipe 50 of the present disclosure was finalized for each of the offline manufacturing system 10 of FIG. 1 and a manufacturing line 102 of a manufacturing plant 100 of FIG. 12, as explained more below. In particular, and as set forth in FIG. 7A, the filling recipe 50 includes specific needle parameters, including setting a needle setting dimension to one of 134.5 mm and 39.0 mm, setting a basic needle position to 7.0 mm, and setting the start needle down to 25 degrees. In addition, the needle parameters for the filling recipe 50 also include setting the needle at a dosing start of 10 mm, setting the needle down to one of 60 degrees and 23 degrees, and setting the needle up at 125 degrees. Further, the filling recipe 50 also includes setting the needle at the end of dosing to 13.0 mm and 310 degrees, setting the start needle to cut-off position of 315 degrees, setting the cut off position reached to 13.0 mm and 315 degrees, setting the start needle to a basic position of 315 degrees, and the basic needle position reached to 359 degrees.

[0062] In addition, and as set forth in FIG. 7B, the finalized filling recipe 50 of the present disclosure also includes setting several parameters for the pump. In particular, the filling recipe 50 includes setting the start pump dosing to 40 degrees, setting the pump dosing start ramp to 90 degrees, setting the pump dosing stop ramp to 210 degrees, and setting the end pump dosing to 260 degrees. Further, the filling recipe includes setting the drip retraction parameter to 20 degrees, such as the pump distance run for the drip retraction to 20 degrees, the end drip retraction parameter to 290 degrees, and the distance run per dose parameter to 766 degrees. In another example, and more generally, the filling recipe 50 may include setting the drip retraction parameter to any value equal to or less than 20 degrees and still fall within the scope of the present disclosure. In one example, the lowest value of the drip retraction parameter is 0 degrees. In another example, the filling recipe 50 may include setting the drip retraction parameter for the pump to one of 10 degrees, 20 degrees, or any value in a range of 10 degrees to 20 degrees.

Still further, the filling recipe 50 may include setting the end drip retraction to 290 degrees when the drip retraction parameter is set to 20 degrees, or setting the end drip retraction value to 280 when setting the drip retraction parameter to 10 degrees, for example. Said another way, depending upon the value selected for the drip retraction parameter, e.g., any value equal to or less than 20 degrees, the end drip retraction parameter will be adjusted and set accordingly to be consistent with the set drip retraction parameter value. In addition, the finalized filling recipe 50 also includes setting a no adjustment limit for the fill weight of any vial to T1, with T1 being at or in a range of about 2% more or 2% less than a fill weight of a target fill weight T0, as explained above relative to FIG. 3B, for example.

[0063] While this filling recipe 50 was finalized for the exemplary drug product DP1 in the second fill set 16, the same filling recipe 50 may also be used for the first fill set 14 using DP1 or other drug products in the mAb formulation programs, for example. Still further, and as explained more below, the same finalized filling recipe 50 is also effectively used for a nested syringe and vial line of a manufacturing plant. More generally, the method of optimizing a filling recipe for a nested syringe and vial line or other manufacturing line in a manufacturing plant includes using the first and second fill sets 14, 16 of the offline manufacturing system 1 of FIG. 1, for example.

[0064] Referring now to FIGS. 8A and 8B, the impact of temperature on fill performance of the second fill set 16 was evaluated for efficacy and the results are provided in the graph of FIG. 8A and the table of FIG. 8B. In particular, for this experimental cycle, the temperature was set at 10-11 degrees Celsius and the process performance parameter Cpk during this temperature range of 10-11 degrees Celsius throughout the fill cycle well exceeded a minimum value of 1.33. In particular, the cycle included 103 fills, with a minimum fill weight of 1.340 g, a maximum fill weight of 1.393 g, and an average fill weight of 1.362 g with a standard deviation of 0.008 grams. Further, the process performance parameter Cpk value was 1.95, well above the target minimum value of 1.33, for example. While FIG. 8A shows that occasional filling weights were close to the T1 limits at this temperature range, subsequent fill weights were able to return close to the target without significantly impacting the process performance index Cpk.

[0065] Referring now to FIGS. 9A and 9B, the impact of a temperature higher than 10-11 degrees Celsius (as in FIGS. 8A and 8B) on fill performance of the second fill set 16 was evaluated, and the results are provided in the graph of FIG. 9A and the table of FIG. 9B. In particular, for this experimental cycle, the temperature was set at about 19 degrees Celsius, and the process performance parameter Cpk during this temperature of about 19 degrees Celsius throughout the fill cycle well exceeded a minimum value of 1.33. Specifically, the cycle included 103 fills, with a minimum fill weight of 1.348 g, a maximum fill weight of 1.384 g, and an average fill weight of 1.366 g with a standard deviation of 0.006 grams. Further, the process performance parameter Cpk against T2 was 2.69, well above both the target minimum value of 1.3, and the process performance parameter Cpk for the fill performance at the lower temperature of 10-11 degrees Celsius, in this example. This indicates an even better fill performance for the finalized filling recipe at slightly higher temperatures.

[0066] Referring now to FIGS. 10A and 10B, the impact of a temperature on fill performance of the first fill set 14 was evaluated, and the results are provided in the graph of FIG. 10A and the table of FIG. 10B. In particular, for this experimental cycle, the temperature was set at about a range of 10-11 degrees Celsius, and the process performance parameter Cpk during this temperature throughout the fill cycle well exceeded a minimum value, such as 1.33. Specifically, the cycle included 100 fills, with a minimum fill weight of 1.354 g, a maximum fill weight of 1.380 g, and an average fill weight of 1.365 g with a standard deviation of 0.005 grams. Further, the process performance parameter Cpk against T2 was 3.16, well above each of the target minimum value of 1.33, and the process performance parameter Cpk for the fill performance of the second fill set 16 at both the lower temperature of 10-11 degrees Celsius (FIGS. 8A and 8B) and the higher temperature 19 degrees Celsius (FIGS. 9A and 9B), for example. Thus, such results further show the universal nature and applicability of the finalized filling recipe on different

fill sets, and this filling recipe may also be successfully transferred and used with a nested syringe and vial line of a manufacturing plant, for example.

[0067] Referring now to FIGS. 11A and 11B, the impact of a temperature higher than 10-11 degrees Celsius (as in FIGS. 10A and 10B) on fill performance of the first fill set 14 was evaluated, and the results are provided in the graph of FIG. 11A and the table of FIG. 11B. In particular, for this experimental cycle, the temperature was set at about 19 degrees Celsius and the process performance parameter Cpk during this temperature of about 19 degrees Celsius throughout the fill cycle well exceeded a minimum value of 1.33. Specifically, the cycle included 120 fills, with a minimum fill weight of 1.352 g, a maximum fill weight of 1.373 g, and an average fill weight of 1.362 g with a standard deviation of 0.004 grams. Further, the process performance parameter Cpk against T2 was 3.61, well above both the target minimum value of 1.33, and the process performance parameter Cpk of 3.16 for the fill performance at the lower temperature of 10-11 degrees Celsius, for example.

[0068] Thus, the results show that there is superior fill weight performance with the first set 14 of FIGS. 10A-11B compared to the fill performance of the second fill set 16 of FIGS. 8A-9B, although the minimum process performance index Cpk is exceeded for all temperature ranges of both the first and second sets 14, 16. In addition, the temperature effect observed with the second fill set 16 is less pronounced in the first fill set 14.

[0069] Referring now to FIG. 12, a schematic representation of a manufacturing line 102 in a manufacturing plant 100 is depicted. In this example, the manufacturing line 102 includes at least one nested syringe and vial line 104 in which the efficient universal filling recipe 50 of the present disclosure is effectively used. In one example, the nested syringe and vial line 104 is a nested syringe and vial line (NSVL) having a plurality of vials 105, such as ISO 2R RTU vials. It will be understood that the filling recipe 50 of the present disclosure may be utilized in a variety of other nested syringe and vial lines and still fall within the scope of the present disclosure. It will also be understood that the vial 105 may more generally be any container 105, such as a syringe, and still fall within the scope of the present disclosure. In addition, in other examples, the manufacturing line 102 may include a plurality of nested syringe and vial lines 106, each of which includes the at least one nested syringe and vial line 104, for example. The manufacturing line 102 also includes at least one pump 110 that corresponds to and cooperates with at least one vial of the at least one nested syringe and vial line 104. In addition, there may also be a plurality of pumps 112 that correspond to a plurality of vials 114 of the nested syringe and vial line 104. In still other examples, there may be a plurality of nested syringe and vial lines in which the filling recipe 50 of the present disclosure is implemented.

[0070] Referring now to FIGS. 13A and 13B, an exemplary nested syringe and vial line 104 of FIG. 12 is depicted in FIG. 13A. The nested syringe and vial line 104 is a B20 nested syringe and vial line (NSVL) that includes a semi-automated debagger 104a, an automated debagger 104b, a rapid transfer airlock 104c, a nested filler (isolator) 104d, and a capper 104e. Various other clinical or commercial manufacturing fillers may alternatively be used and still fall within the scope of the present disclosure.

[0071] In addition, FIG. 13B depicts a plurality of pumps, which may be the plurality of pumps 112 that correspond to the plurality of vials 114 of the nested syringe and vial line 104 of FIG. 12, for example. In this example, the plurality of pumps 112 include five pumps 110 that cooperate with each vial 105 of the plurality of vials 114. In this example, the nested syringe and vial line 104 is a clinical manufacturing filler, such as a Bausch & Strobel filler. While the containers 105 are referred to generally as vials, it will be understood that the containers 105 may be one or more of vials, syringes or plastic cartridges and still fall within the scope of the present disclosure. For example, the containers 105 may include nested ISO 2R vials, nested 1mL glass and plastic syringes, or nested 5cc plastic cartridges. In addition, while the plurality of pumps include five pumps 110 in this example, it will be understood that more or fewer pumps may alternatively be used and still fall within the scope of the present disclosure. In one example, the plurality of pumps may include 10 pumps or 2 pumps for different filler, or any other number of pumps within this range, for example, and still fall within the scope of the present disclosure.

[0072] A method of filling the plurality of vials 105 of the nested syringe and vial line 104 comprises providing one of the pump 110 or a plurality of pumps 112 corresponding to one of the vial 105 or the plurality of vials 105 of the nested syringe and vial line 104. The method also includes setting the drip retraction parameter for each pump 110 to any value equal to or less than 20 degrees. In addition, in one example, the method also includes setting a no adjustment limit for the fill weight of the vial 105 to T1, with T1 being at or in a range of about 2% more or 2% less than the fill weight of the target fill weight T0. The method may still further include filling each vial 105 of the plurality of vials 105 with a drug product, such as a mAb formulation, via a corresponding pump 110 of the plurality of pumps 112. The method may still also include exceeding a minimum value for the process performance index Cpk for each vial 105 of the plurality of vials 105 during a temperature range throughout a fill cycle, the temperature range one of: (1) 5 (+/-3) degrees Celsius; (2) 20 (+/-5) degree Celsius; or (3) 10 to 19 degrees Celsius.

[0073] In this example, the minimum value for the process performance index Cpk is 1.33. In other examples, such as in clinical fills, a minimum value for the process performance index Cpk is 1.0. However, in this example, and as generally understood in commercial fills, the minimum value for the process performance index Cpk is 1.33. In addition, filling each vial 105 with the drug product via the corresponding pump 110 of the plurality of pumps 112 comprises filling each vial 105 with a drug product, wherein the drug product has one or more of the following characteristics: (1) a density in a range of about 1.0-1.2 g/cm³; (b) a viscosity in a range of about 1.0-10.0 cP; and (c) a surface tension in a range of about 40.0-72.7 mN/m. In one example, the drug product has a density in a range of 1.0-1.2 g/cm³; a viscosity in a range of about 1.0-10.0 cP; and a surface tension in a range of about 40.0-72.7 mN/m.

[0074] Referring now to FIGS. 14 and 15, the fill performance of the new filling recipe of the present disclosure in the nested syringe and vial line 104 is provided. In particular, using the new filling recipe, the total dose optimization cycle, such as the number of strokes of the pump 110 (or pumps 112) needed to teach the pump 110 how to operate using the new filling recipe is minimized. Specifically, the total dose optimization cycle value is 4, which is significantly reduced compared to values of the total dose optimization cycle of previous filling recipes set forth in FIG. 15, for example. In addition, the process performance index Cpk for each nozzle (not shown) of each pump 110 of the plurality of pumps 112 of the nested syringe and vial line 104 (of FIG. 12) exceeds the minimum value of 1.33 for the process performance index Cpk desired. In fact, the average process performance index Cpk value for all nozzles of the pumps 110 is 1.4.

[0075] Referring now to FIG. 15, a chart listing the process performance index Cpk of nozzles of the pumps using old filling recipes is set forth. Specifically, when using old filling recipes for a large variety of different drug products, including the mAb formulations, the average process performance index Cpk for all nozzles of the pumps was well below the desired process performance index Cpk value of 1.33. Said another way, all of the process performance index Cpk values were less than 1.33. In addition, the total dose optimization cycle was greater for each drug product using the old filling recipe compared to the dose optimization cycle value listed in FIG. 14 when using the new filling recipe 50.

[0076] In view of the foregoing, it will be appreciated that a method of optimizing a filling recipe for a container, such as the vial 105 of the nested syringe and vial line 104, was finalized using the first and second fill sets 14, 16 and corresponding first and second fill targets 18, 20 of an offline manufacturing system 10 described above and depicted in FIG. 1, for example. By finalizing the recipe using an offline system, such as the offline system 10, a team of scientists is able to run experiments and tests unable to be conducted in a large scale manufacturing plant such that the manufacturing line within the manufacturing plant is not displaced or interrupted. In addition, the offline systems 10 often include cameras and do not include the limitations of needed operator gear and other restrictions of a large-scale manufacturing plant. Further, this same optimized filling recipe may be used for different drug products, as described above.

[0077] More specifically, the method of optimizing the filling recipe for the nested syringe and vial line 104 includes setting the drip retraction parameter for at least one pump 14, 16, 22 in the offline manufacturing system 10 corresponding to at least one container 18, 20 to any value equal to or less than 20 degrees. The method further includes monitoring a performance of the at least one pump 14, 16, 20 with the drip retraction parameter of the at least one pump 14, 16, 22 set to any value equal to or less than 20 degrees. The method still further includes obtaining at least a minimum value for the process performance index (Cpk) for the at least one container 18, 20 throughout at least one fill cycle and for at least one drug product using the at least one pump 14, 16, 22 in the offline manufacturing system 10. The method also includes finalizing a filling recipe for the nested syringe and vial line 104 using data from fill cycles of the at least one drug product using the at least one pump 14, 16, 22 in the offline manufacturing system 10.

[0078] Thus, an optimized filling recipe for drug products, such as mAb drug products, has been developed that is applicable to manufacturing lines in a manufacturing plant. As a result, significant time related to programming of pumps corresponding to a nested syringe and vial line of the manufacturing plant (e.g., often needed for different recipes for different drug products) is saved.

[0079] The above description describes various systems and methods of filling a vial of a nested syringe and vial line. It should be clear that the system or methods can further comprise use of a medicament listed below with the caveat that the following list should neither be considered to be all inclusive nor limiting. The medicament will be contained in a reservoir. In some instances, the reservoir is a primary container that is either filled for treatment with the medicament. The primary container can be a vial, a cartridge or a syringe.

[0080] For example, drug products that may be used with the methods disclosed herein may include colony stimulating factors, such as granulocyte colony-stimulating factor (G-CSF). Such G-CSF agents include, but are not limited to, Neupogen® (filgrastim) and Neulasta® (pegfilgrastim). In various other embodiments, the methods may use various pharmaceutical products, such as an erythropoiesis stimulating agent (ESA), which may be in a liquid or a lyophilized form. An ESA is any molecule that stimulates erythropoiesis, such as Epogen® (epoetin alfa), Aranesp® (darbepoetin alfa), Dynepo® (epoetin delta), Mircera® (methoxy polyethylene glycol-epoetin beta), Hematide®, MRK-2578, INS-22, Retacrit® (epoetin zeta), Neorecormon® (epoetin beta), Silapo® (epoetin zeta), Binocrit® (epoetin alfa), epoetin alfa Hexal, Abseamed® (epoetin alfa), Ratioepo® (epoetin theta), Eporatio® (epoetin theta), Biopoin® (epoetin theta), epoetin alfa, epoetin beta, epoetin zeta, epoetin theta, and epoetin delta, as well as the molecules or variants or analogs thereof as disclosed in the following patents or patent applications, each of which is herein incorporated by reference in its entirety: U.S. Patent Nos. 4,703,008; 5,441,868; 5,547,933; 5,618,698; 5,621,080; 5,756,349; 5,767,078; 5,773,569; 5,955,422; 5,986,047; 6,583,272; 7,084,245; and 7,271,689; and PCT Publication Nos. WO 91/05867; WO 95/05465; WO 96/40772; WO 00/24893; WO 01/81405; and WO 2007/136752.

[0081] An ESA can be an erythropoiesis stimulating protein. As used herein, "erythropoiesis stimulating protein" means any protein that directly or indirectly causes activation of the erythropoietin receptor, for example, by binding to and causing dimerization of the receptor. Erythropoiesis stimulating proteins include erythropoietin and variants, analogs, or derivatives thereof that bind to and activate erythropoietin receptor; antibodies that bind to erythropoietin receptor and activate the receptor; or peptides that bind to and activate erythropoietin receptor. Erythropoiesis stimulating proteins include, but are not limited to, epoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin iota, epoetin zeta, and analogs thereof, pegylated erythropoietin, carbamylated erythropoietin, mimetic peptides (including EMP1/hematide), and mimetic antibodies. Exemplary erythropoiesis stimulating proteins include erythropoietin, darbepoetin, erythropoietin agonist variants, and peptides or antibodies that bind and activate erythropoietin receptor (and include compounds reported in U.S. Publication Nos. 2003/0215444 and 2006/0040858, the disclosures of each of which is incorporated herein by reference in its entirety) as well as erythropoietin

molecules or variants or analogs thereof as disclosed in the following patents or patent applications, which are each herein incorporated by reference in its entirety: U.S. Patent Nos. 4,703,008; 5,441,868; 5,547,933; 5,618,698; 5,621,080; 5,756,349; 5,767,078; 5,773,569; 5,955,422; 5,830,851; 5,856,298; 5,986,047; 6,030,086; 6,310,078; 6,391,633; 6,583,272; 6,586,398; 6,900,292; 6,750,369; 7,030,226; 7,084,245; and 7,217,689; U.S. Publication Nos. 2002/0155998; 2003/0077753; 2003/0082749; 2003/0143202; 2004/0009902; 2004/0071694; 2004/0091961; 2004/0143857; 2004/0157293; 2004/0175379; 2004/0175824; 2004/0229318; 2004/0248815; 2004/0266690; 2005/0019914; 2005/0026834; 2005/0096461; 2005/0107297; 2005/0107591; 2005/0124045; 2005/0124564; 2005/0137329; 2005/0142642; 2005/0143292; 2005/0153879; 2005/0158822; 2005/0158832; 2005/0170457; 2005/0181359; 2005/0181482; 2005/0192211; 2005/0202538; 2005/0227289; 2005/0244409; 2006/0088906; and 2006/0111279; and PCT Publication Nos. WO 91/05867; WO 95/05465; WO 99/66054; WO 00/24893; WO 01/81405; WO 00/61637; WO 01/36489; WO 02/014356; WO 02/19963; WO 02/20034; WO 02/49673; WO 02/085940; WO 03/029291; WO 2003/055526; WO 2003/084477; WO 2003/094858; WO 2004/002417; WO 2004/002424; WO 2004/009627; WO 2004/024761; WO 2004/033651; WO 2004/035603; WO 2004/043382; WO 2004/101600; WO 2004/101606; WO 2004/101611; WO 2004/106373; WO 2004/018667; WO 2005/001025; WO 2005/001136; WO 2005/021579; WO 2005/025606; WO 2005/032460; WO 2005/051327; WO 2005/063808; WO 2005/063809; WO 2005/070451; WO 2005/081687; WO 2005/084711; WO 2005/103076; WO 2005/100403; WO 2005/092369; WO 2006/50959; WO 2006/02646; and WO 2006/29094.

[0082] Examples of other pharmaceutical products that may be used with the methods disclosed herein may include, but are not limited to, antibodies such as Vectibix® (panitumumab), Xgeva™ (denosumab) and Prolia™ (denosumab); other biological agents such as Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker), Neulasta® (pegfilgrastim, pegylated filgrastim, pegylated G-CSF, pegylated hu-Met-G-CSF), Neupogen® (filgrastim, G-CSF, hu-MetG-CSF), and Nplate® (romiplostim); small molecule drugs such as Sensipar® (cinacalcet). The methods may also be used with a therapeutic antibody, a polypeptide, a protein or other chemical, such as an iron, for example, ferumoxyl, iron dextrans, ferric glyconate, and iron sucrose. The pharmaceutical product may be in liquid form, or reconstituted from lyophilized form.

[0083] Among particular illustrative proteins are the specific proteins set forth below, including fusions, fragments, analogs, variants or derivatives thereof: OPGL specific antibodies, peptibodies, and related proteins, and the like (also referred to as RANKL specific antibodies, peptibodies and the like), including fully humanized and human OPGL specific antibodies, particularly fully humanized monoclonal antibodies, including but not limited to the antibodies described in PCT Publication No. WO 03/002713, which is incorporated herein in its entirety as to OPGL specific antibodies and antibody related proteins, particularly those having the sequences set forth therein, particularly, but not limited to, those denoted therein: 9H7; 18B2; 2D8; 2E11; 16E1; and 22B3, including the OPGL specific antibodies having either the light chain of SEQ ID NO:2 as set forth therein in Figure 2 and/or the heavy chain of SEQ ID NO:4, as set forth therein in Figure 4, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[0084] Myostatin binding proteins, peptibodies, and related proteins, and the like, including myostatin specific peptibodies, particularly those described in U.S. Publication No. 2004/0181033 and PCT Publication No. WO 2004/058988, which are incorporated by reference herein in their entirety particularly in parts pertinent to myostatin specific peptibodies, including but not limited to peptibodies of the mTN8-19 family, including those of SEQ ID NOS:305-351, including TN8-19-1 through TN8-19-40, TN8-19 con1 and TN8-19 con2; peptibodies of the mL2 family of SEQ ID NOS:357-383; the mL15 family of SEQ ID NOS:384-409; the mL17 family of SEQ ID NOS:410-438; the mL20 family of SEQ ID NOS:439-446; the mL21 family of SEQ ID NOS:447-452; the mL24 family of SEQ ID NOS:453-454; and those of SEQ ID NOS:615-631, each of which is individually and specifically incorporated by reference herein in their entirety fully as disclosed in the foregoing publication;

[0085] IL-4 receptor specific antibodies, peptibodies, and related proteins, and the like, particularly those that inhibit activities mediated by binding of IL-4 and/or IL-13 to the receptor, including those described in PCT Publication No. WO 2005/047331 or PCT Application No. PCT/US2004/37242 and in U.S. Publication No. 2005/112694, which are incorporated herein by reference in their entirety particularly in parts pertinent to IL-4 receptor specific antibodies, particularly such antibodies as are described therein, particularly, and without limitation, those designated therein: L1H1; L1H2; L1H3; L1H4; L1H5; L1H6; L1H7; L1H8; L1H9; L1H10; L1H11; L2H1; L2H2; L2H3; L2H4; L2H5; L2H6; L2H7; L2H8; L2H9; L2H10; L2H11; L2H12; L2H13; L2H14; L3H1; L4H1; L5H1; L6H1, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[0086] Interleukin 1-receptor 1 ("IL1-R1") specific antibodies, peptibodies, and related proteins, and the like, including but not limited to those described in U.S. Publication No. 2004/097712, which is incorporated herein by reference in its entirety in parts pertinent to IL1-R1 specific binding proteins, monoclonal antibodies in particular, especially, without limitation, those designated therein: 15CA, 26F5, 27F2, 24E12, and 10H7, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the aforementioned publication;

[0087] Ang2 specific antibodies, peptibodies, and related proteins, and the like, including but not limited to those described in PCT Publication No. WO 03/057134 and U.S. Publication No. 2003/0229023, each of which is incorporated herein by reference in its entirety particularly in parts pertinent to Ang2 specific antibodies and peptibodies and the like, especially those of sequences described therein and including but not limited to: L1(N); L1(N) WT; L1(N) 1K WT; 2xL1(N); 2xL1(N) WT; Con4 (N), Con4 (N) 1K WT, 2xCon4 (N) 1K; L1C; L1C 1K; 2xL1C; Con4C; Con4C 1K; 2xCon4C 1K; Con4-L1 (N); Con4-L1C; TN-12-9 (N); C17 (N); TN8-8(N); TN8-14 (N); Con 1 (N), also including anti-Ang 2 antibodies and formulations such as those described in PCT Publication No. WO 2003/030833 which is incorporated herein by reference in its entirety as to the same, particularly Ab526; Ab528; Ab531; Ab533; Ab535; Ab536; Ab537; Ab540; Ab543; Ab544; Ab545; Ab546; A551; Ab553; Ab555; Ab558; Ab559; Ab565; AbF1AbFD; AbFE; AbFJ; AbFK; AbG1D4; AbGC1E8; AbH1C12; AbIA1; AbIF; AbIK; AbIP; and AbIP, in their various permutations as described therein, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[0088] NGF specific antibodies, peptibodies, and related proteins, and the like including, in particular, but not limited to those described in U.S. Publication No. 2005/0074821 and U.S. Patent No. 6,919,426, which are incorporated herein by reference in their entirety particularly as to NGF-specific antibodies and related proteins in this regard, including in particular, but not limited to, the NGF-specific antibodies therein designated 4D4, 4G6, 6H9, 7H2, 14D10 and 14D11, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[0089] CD22 specific antibodies, peptibodies, and related proteins, and the like, such as those described in U.S. Patent No. 5,789,554, which is incorporated herein by reference in its entirety as to CD22 specific antibodies and related proteins, particularly human CD22 specific antibodies, such as but not limited to humanized and fully human antibodies, including but not limited to humanized and fully human monoclonal antibodies, particularly including but not limited to human CD22 specific IgG antibodies, such as, for instance, a dimer of a human-mouse monoclonal hLL2 gamma-chain disulfide linked to a human-mouse monoclonal hLL2 kappa-chain, including, but limited to, for example, the human CD22 specific fully humanized antibody in Epratuzumab, CAS registry number 501423-23-0;

[0090] IGF-1 receptor specific antibodies, peptibodies, and related proteins, and the like, such as those described in PCT Publication No. WO 06/069202, which is incorporated herein by reference in its entirety as to IGF-1 receptor specific antibodies and related proteins, including but not limited to the IGF-1 specific antibodies therein designated L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20,

L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, L52H52, and IGF-1R-binding fragments and derivatives thereof, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[0091] Also among non-limiting examples of anti-IGF-1R antibodies for use in the methods and compositions of the present invention are each and all of those described in:

[0092] (i) U.S. Publication No. 2006/0040358 (published February 23, 2006), 2005/0008642 (published January 13, 2005), 2004/0228859 (published November 18, 2004), including but not limited to, for instance, antibody 1A (DSMZ Deposit No. DSM ACC 2586), antibody 8 (DSMZ Deposit No. DSM ACC 2589), antibody 23 (DSMZ Deposit No. DSM ACC 2588) and antibody 18 as described therein;

[0093] (ii) PCT Publication No. WO 06/138729 (published December 28, 2006) and WO 05/016970 (published February 24, 2005), and Lu et al. (2004), J. Biol. Chem. 279:2856-2865, including but not limited to antibodies 2F8, A12, and IMC-A12 as described therein;

[0094] (iii) PCT Publication No. WO 07/012614 (published February 1, 2007), WO 07/000328 (published January 4, 2007), WO 06/013472 (published February 9, 2006), WO 05/058967 (published June 30, 2005), and WO 03/059951 (published July 24, 2003)

[0095] (iv) U.S. Publication No. 2005/0084906 (published April 21, 2005), including but not limited to antibody 7C10, chimaeric antibody C7C10, antibody h7C10, antibody 7H2M, chimaeric antibody *7C10, antibody GM 607, humanized antibody 7C10 version 1, humanized antibody 7C10 version 2, humanized antibody 7C10 version 3, and antibody 7H2HM, as described therein;

[0096] (v) U.S. Publication Nos. 2005/0249728 (published November 10, 2005), 2005/0186203 (published August 25, 2005), 2004/0265307 (published December 30, 2004), and 2003/0235582 (published December 25, 2003) and Maloney et al. (2003), Cancer Res. 63:5073-5083, including but not limited to antibody EM164, resurfaced EM164, humanized EM164, huEM164 v1.0, huEM164 v1.1, huEM164 v1.2, and huEM164 v1.3 as described therein;

[0097] (vi) U.S. Patent No. 7,037,498 (issued May 2, 2006), U.S. Publication Nos. 2005/0244408 (published November 30, 2005) and 2004/0086503 (published May 6, 2004), and Cohen, et al. (2005), Clinical Cancer Res. 11:2063-2073, e.g., antibody CP-751,871, including but not limited to each of the antibodies produced by the hybridomas having the ATCC accession numbers PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789, PTA-2793, and antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, and 4.17.3, as described therein;

[0098] (vii) U.S. Publication Nos. 2005/0136063 (published June 23, 2005) and 2004/0018191 (published January 29, 2004), including but not limited to antibody 19D12 and an antibody comprising a heavy chain encoded by a polynucleotide in plasmid 15H12/19D12 HCA (γ4), deposited at the ATCC under number PTA-5214, and a light chain encoded by a polynucleotide in plasmid 15H12/19D12 LCF (κ), deposited at the ATCC under number PTA-5220, as described therein; and

[0099] (viii) U.S. Publication No. 2004/0202655 (published October 14, 2004), including but not limited to antibodies PINT-6A1, PINT-7A2, PINT-7A4, PINT-7A5, PINT-7A6, PINT-8A1, PINT-9A2, PINT-11A1, PINT-11A2, PINT-11A3, PINT-11A4, PINT-11A5, PINT-11A7, PINT-11A12, PINT-12A1, PINT-12A2, PINT-12A3, PINT-12A4, and PINT-12A5, as described therein; each and all of which are herein incorporated by reference in their entireties, particularly as to the aforementioned antibodies, peptibodies, and related proteins and the like that target IGF-1 receptors;

[00100] B-7 related protein 1 specific antibodies, peptibodies, related proteins and the like ("B7RP-1," also is referred to in the literature as B7H2, ICOSL, B7h, and CD275), particularly B7RP-specific fully human monoclonal IgG2 antibodies, particularly fully human IgG2 monoclonal antibody that binds an epitope in the first immunoglobulin-like domain of B7RP-1, especially those that inhibit the interaction of B7RP-1 with its natural receptor, ICOS, on activated T cells in particular, especially, in all of the foregoing regards, those disclosed in U.S. Publication No. 2008/0166352 and PCT Publication No. WO 07/011941, which are incorporated herein by reference in their entireties as to such antibodies and related proteins, including but not limited to antibodies designated therein as follow: 16H (having light chain variable and heavy chain variable sequences SEQ ID NO:1 and SEQ ID NO:7 respectively therein); 5D (having light chain variable and heavy chain variable sequences SEQ ID NO:2 and SEQ ID NO:9 respectively therein); 2H (having light chain variable and heavy chain variable sequences SEQ ID NO:3 and SEQ ID NO:10 respectively therein); 43H (having light chain variable and heavy chain variable sequences SEQ ID NO:6 and SEQ ID NO:14 respectively therein); 41H (having light chain variable and heavy chain variable sequences SEQ ID NO:5 and SEQ ID NO:13 respectively therein); and 15H (having light chain variable and heavy chain variable sequences SEQ ID NO:4 and SEQ ID NO:12 respectively therein), each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[00101] IL-15 specific antibodies, peptibodies, and related proteins, and the like, such as, in particular, humanized monoclonal antibodies, particularly antibodies such as those disclosed in U.S. Publication Nos. 2003/0138421; 2003/023586; and 2004/0071702; and U.S. Patent No. 7,153,507, each of which is incorporated herein by reference in its entirety as to IL-15 specific antibodies and related proteins, including peptibodies, including particularly, for instance, but not limited to, HuMax IL-15 antibodies and related proteins, such as, for instance, 146B7;

[00102] IFN gamma specific antibodies, peptibodies, and related proteins and the like, especially human IFN gamma specific antibodies, particularly fully human anti-IFN gamma antibodies, such as, for instance, those described in U.S. Publication No. 2005/0004353, which is incorporated herein by reference in its entirety as to IFN gamma specific antibodies, particularly, for example, the antibodies therein designated 1118; 1118*; 1119; 1121; and 1121*. The entire sequences of the heavy and light chains of each of these antibodies, as well as the sequences of their heavy and light chain variable regions and complementarity determining regions, are each individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication and in Thakur et al. (1999), Mol. Immunol. 36:1107-1115. In addition, description of the properties of these antibodies provided in the foregoing publication is also incorporated by reference herein in its entirety. Specific antibodies include those having the heavy chain of SEQ ID NO:17 and the light chain of SEQ ID NO:18; those having the heavy chain variable region of SEQ ID NO:6 and the light chain variable region of SEQ ID NO:8; those having the heavy chain of SEQ ID NO:19 and the light chain of SEQ ID NO:20; those having the heavy chain variable region of SEQ ID NO:10 and the light chain variable region of SEQ ID NO:12; those having the heavy chain of SEQ ID NO:32 and the light chain of SEQ ID NO:20; those having the heavy chain variable region of SEQ ID NO:30 and the light chain variable region of SEQ ID NO:12; those having the heavy chain sequence of SEQ ID NO:21 and the light chain sequence of SEQ ID NO:22; those having the heavy chain variable region of SEQ ID NO:14 and the light chain variable region of SEQ ID NO:16; those having the heavy chain of SEQ ID NO:21 and the light chain of SEQ ID NO:33; and those having the heavy chain variable region of SEQ ID NO:14 and the light chain variable region of SEQ ID NO:31, as disclosed in the foregoing publication. A specific antibody contemplated is antibody 1119 as disclosed in the foregoing U.S. publication and having a complete heavy chain of SEQ ID NO:17 as disclosed therein and having a complete light chain of SEQ ID NO:18 as disclosed therein;

[00103] TALL-1 specific antibodies, peptibodies, and the related proteins, and the like, and other TALL specific binding proteins, such as those described in U.S. Publication Nos. 2003/0195156 and 2006/0135431, each of which is incorporated

herein by reference in its entirety as to TALL-1 binding proteins, particularly the molecules of Tables 4 and 5B, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publications;

[00104] Parathyroid hormone ("PTH") specific antibodies, peptibodies, and related proteins, and the like, such as those described in U.S. Patent No. 6,756,480, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind PTH;

[00105] Thrombopoietin receptor ("TPO-R") specific antibodies, peptibodies, and related proteins, and the like, such as those described in U.S. Patent No. 6,835,809, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind TPO-R;

[00106] Hepatocyte growth factor ("HGF") specific antibodies, peptibodies, and related proteins, and the like, including those that target the HGF/SF:cMet axis (HGF/SF:c-Met), such as the fully human monoclonal antibodies that neutralize hepatocyte growth factor/scatter (HGF/SF) described in U.S. Publication No. 2005/0118643 and PCT Publication No. WO 2005/017107, huL2G7 described in U.S. Patent No. 7,220,410 and OA-5d5 described in U.S. Patent Nos. 5,686,292 and 6,468,529 and in PCT Publication No. WO 96/38557, each of which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind HGF;

[00107] TRAIL-R2 specific antibodies, peptibodies, related proteins and the like, such as those described in U.S. Patent No. 7,521,048, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind TRAIL-R2;

[00108] Activin A specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in U.S. Publication No. 2009/0234106, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind Activin A;

[00109] TGF-beta specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in U.S. Patent No. 6,803,453 and U.S. Publication No. 2007/0110747, each of which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind TGF-beta;

[00110] Amyloid-beta protein specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in PCT Publication No. WO 2006/081171, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind amyloid-beta proteins. One antibody contemplated is an antibody having a heavy chain variable region comprising SEQ ID NO:8 and a light chain variable region having SEQ ID NO:6 as disclosed in the foregoing publication;

[00111] c-Kit specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in U.S. Publication No. 2007/0253951, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind c-Kit and/or other stem cell factor receptors;

[00112] OX40L specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in U.S. Publication No. 2006/0002929, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind OX40L and/or other ligands of the OX40 receptor; and

[00113] Other exemplary proteins, including Activase® (alteplase, tPA); Aranesp® (darbepoetin alfa); Epogen® (epoetin alfa, or erythropoietin); GLP-1, Avonex® (interferon beta-1a); Bexxar® (tositumomab, anti-CD22 monoclonal antibody); Betaseron® (interferon-beta); Campath® (alemtuzumab, anti-CD52 monoclonal antibody); Dynepo® (epoetin delta); Velcade® (bortezomib); MLN0002 (anti- α4β7 mAb); MLN1202 (anti-CCR2 chemokine receptor mAb); Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker); Eprex® (epoetin alfa); Erbitux® (cetuximab, anti-EGFR / HER1 / c-ErbB-1); Genotropin® (somatropin, Human Growth Hormone); Herceptin® (trastuzumab, anti-HER2/neu (erbB2) receptor mAb); Humatrope® (somatropin, Human

Growth Hormone); Humira® (adalimumab); insulin in solution; Infergen® (interferon alfacon-1); Natrecor® (nesiritide); recombinant human B-type natriuretic peptide (hBNP); Kineret® (anakinra); Leukine® (sargamostim, rhuGM-CSF); LymphoCide® (epratuzumab, anti-CD22 mAb); Benlysta™ (lymphostatin B, belimumab, anti-BlyS mAb); Metalyse® (tenecteplase, t-PA analog); Mircera® (methoxy polyethylene glycol-epoetin beta); Mylotarg® (gemtuzumab ozogamicin); Raptiva® (efalizumab); Cimzia® (certolizumab pegol, CDP 870); Soliris™ (eculizumab); pexelizumab (anti-C5 complement); Numax® (MEDI-524); Lucentis® (ranibizumab); Panorex® (17-1A, edrecolomab); Trabio® (lerdelimumab); TheraCim hR3 (nimotuzumab); Omnitarg (pertuzumab, 2C4); Osidem® (IDM-1); OvaRex® (B43.13); Nuvion® (visilizumab); cantuzumab mertansine (huC242-DM1); NeoRecormon® (epoetin beta); Neumega® (oprelvekin, human interleukin-11); Neulasta® (pegylated filgrastim, pegylated G-CSF, pegylated hu-Met-G-CSF); Neupogen® (filgrastim, G-CSF, hu-MetG-CSF); Orthoclone OKT3® (muromonab-CD3, anti-CD3 monoclonal antibody); Procrit® (epoetin alfa); Remicade® (infliximab, anti-TNF α monoclonal antibody); Reopro® (abciximab, anti-GP IIb/IIIa receptor monoclonal antibody); Actemra® (anti-IL6 Receptor mAb); Avastin® (bevacizumab), HuMax-CD4 (zanolimumab); Rituxan® (rituximab, anti-CD20 mAb); Tarceva® (erlotinib); Roferon-A® (interferon alfa-2a); Simulect® (basiliximab); Prexige® (lumiracoxib); Synagis® (palivizumab); 146B7-CHO (anti-IL15 antibody, see U.S. Patent No. 7,153,507); Tysabri® (natalizumab, anti- α 4 integrin mAb); Valortim® (MDX-1303, anti-B. anthracis protective antigen mAb); ABthrax™; Vectibix® (panitumumab); Xolair® (omalizumab); ETI211 (anti-MRSA mAb); IL-1 trap (the Fc portion of human IgG1 and the extracellular domains of both IL-1 receptor components (the Type I receptor and receptor accessory protein)); VEGF trap (Ig domains of VEGFR1 fused to IgG1 Fc); Zenapax® (daclizumab); Zenapax® (daclizumab, anti-IL-2R α mAb); Zevalin® (ibritumomab tiuxetan); Zetia® (ezetimibe); Orencia® (atacept, TACI-Ig); anti-CD80 monoclonal antibody (galiximab); anti-CD23 mAb (lumiliximab); BR2-Fc (huBR3 / huFc fusion protein, soluble BAFF antagonist); CNTO 148 (golimumab, anti-TNF α mAb); HGS-ETR1 (mapatumumab; human anti-TRAIL Receptor-1 mAb); HuMax-CD20 (ocrelizumab, anti-CD20 human mAb); HuMax-EGFR (zalutuzumab); M200 (volociximab, anti- α 5 β 1 integrin mAb); MDX-010 (ipilimumab, anti-CTLA-4 mAb and VEGFR-1 (IMC-18F1); anti-BR3 mAb; anti-C. difficile Toxin A and Toxin B C mAbs MDX-066 (CDA-1) and MDX-1388); anti-CD22 dsFv-PE38 conjugates (CAT-3888 and CAT-8015); anti-CD25 mAb (HuMax-TAC); anti-CD3 mAb (NI-0401); adecatumumab; anti-CD30 mAb (MDX-060); MDX-1333 (anti-IFNAR); anti-CD38 mAb (HuMax CD38); anti-CD40L mAb; anti-Cripto mAb; anti-CTGF Idiopathic Pulmonary Fibrosis Phase I Fibrogen (FG-3019); anti-CTLA4 mAb; anti-eotaxin1 mAb (CAT-213); anti-FGF8 mAb; anti-ganglioside GD2 mAb; anti-ganglioside GM2 mAb; anti-GDF-8 human mAb (MYO-029); anti-GM-CSF Receptor mAb (CAM-3001); anti-HepC mAb (HuMax HepC); anti-IFN α mAb (MEDI-545, MDX-1103); anti-IGF1R mAb; anti-IGF-1R mAb (HuMax-Inflam); anti-IL12 mAb (ABT-874); anti-IL12/IL23 mAb (CNTO 1275); anti-IL13 mAb (CAT-354); anti-IL2Ra mAb (HuMax-TAC); anti-IL5 Receptor mAb; anti-integrin receptors mAb (MDX-018, CNTO 95); anti-IP10 Ulcerative Colitis mAb (MDX-1100); anti-LLY antibody; BMS-66513; anti-Mannose Receptor/hCG β mAb (MDX-1307); anti-mesothelin dsFv-PE38 conjugate (CAT-5001); anti-PD1mAb (MDX-1106 (ONO-4538)); anti-PDGFR α antibody (IMC-3G3); anti-TGF β mAb (GC-1008); anti-TRAIL Receptor-2 human mAb (HGS-ETR2); anti-TWEAK mAb; anti-VEGFR/Flt-1 mAb; anti-ZP3 mAb (HuMax-ZP3); NVS Antibody #1; and NVS Antibody #2.

[00114] Also included can be a sclerostin antibody, such as but not limited to romosozumab, blosozumab, or BPS 804 (Novartis). Further included can be therapeutics such as rilatumumab, bixalomer, trebananib, ganitumab, conatumumab, motesanib diphosphate, brodalumab, vidupirant, panitumumab, denosumab, NPLATE, PROLIA, VECTIBIX or XGEVA. Additionally, included in the device can be a monoclonal antibody (IgG) that binds human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), e.g. U.S. Patent No. 8,030,547, U.S. Publication No. 2013/0064825, WO2008/057457, WO2008/057458, WO2008/057459, WO2008/063382, WO2008/133647, WO2009/100297, WO2009/100318, WO2011/037791, WO2011/053759, WO2011/053783, WO2008/125623, WO2011/072263, WO2009/055783, WO2012/0544438, WO2010/029513, WO2011/111007,

WO2010/077854, WO2012/088313, WO2012/101251, WO2012/101252, WO2012/101253, WO2012/109530, and WO2001/031007.

[00115] Also included can be talimogene laherparepvec or another oncolytic HSV for the treatment of melanoma or other cancers. Examples of oncolytic HSV include, but are not limited to talimogene laherparepvec (U.S. Patent Nos. 7,223,593 and 7,537,924); OncoVEXGALV/CD (U.S. Pat. No. 7,981,669); OrienX010 (Lei et al. (2013), *World J. Gastroenterol.*, 19:5138-5143); G207, 1716; NV1020; NV12023; NV1034 and NV1042 (Vargehes et al. (2002), *Cancer Gene Ther.*, 9(12):967-978).

[00116] Also included are TIMPs. TIMPs are endogenous tissue inhibitors of metalloproteinases (TIMPs) and are important in many natural processes. TIMP-3 is expressed by various cells or and is present in the extracellular matrix; it inhibits all the major cartilage-degrading metalloproteases, and may play a role in many degradative diseases of connective tissue, including rheumatoid arthritis and osteoarthritis, as well as in cancer and cardiovascular conditions. The amino acid sequence of TIMP-3, and the nucleic acid sequence of a DNA that encodes TIMP-3, are disclosed in U.S. Patent No. 6,562,596, issued May 13, 2003, the disclosure of which is incorporated by reference herein. Description of TIMP mutations can be found in U.S. Publication No. 2014/0274874 and PCT Publication No. WO 2014/152012.

[00117] Also included are antagonistic antibodies for human calcitonin gene-related peptide (CGRP) receptor and bispecific antibody molecule that target the CGRP receptor and other headache targets. Further information concerning these molecules can be found in PCT Application No. WO 2010/075238.

[00118] Additionally, bispecific T cell engager (BiTE®) molecules, e.g. BLINCYTO® (blinatumomab), can be used in the methods disclosed herein. Alternatively, included can be an APJ large molecule agonist e.g., apelin or analogues thereof in the device. Information relating to such molecules can be found in PCT Publication No. WO 2014/099984.

[00119] In certain embodiments, the medicament comprises a therapeutically effective amount of an anti-thymic stromal lymphopoietin (TSLP) or TSLP receptor antibody. Examples of anti-TSLP antibodies that may be used in such embodiments include, but are not limited to, those described in U.S. Patent Nos. 7,982,016, and 8,232,372, and U.S. Publication No. 2009/0186022. Examples of anti-TSLP receptor antibodies include, but are not limited to, those described in U.S. Patent No. 8,101,182. In particularly preferred embodiments, the medicament comprises a therapeutically effective amount of the anti-TSLP antibody designated as A5 within U.S. Patent No. 7,982,016.

[00120] Although the foregoing methods, and elements thereof, have been described in terms of exemplary embodiments, they are not limited thereto. The detailed description is to be construed as exemplary only and does not describe every possible embodiment of the invention because describing every possible embodiment would be impractical, if not impossible. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent that would still fall within the scope of the claims defining the invention.

[00121] It should be understood that the legal scope of the invention is defined by the words of the claims set forth at the end of this patent. The appended claims should be construed broadly to include other variants and embodiments of same, which may be made by those skilled in the art without departing from the scope and range of equivalents of the devices, systems, methods, and their elements.

What is claimed is:

1. A method of filling a vial, the method comprising:
providing a pump corresponding to a vial;
setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees; and
setting a no adjustment limit for a fill weight of the vial to T1, with T1 being at or in a range of about 2% more or less than a fill weight of a target fill weight T0;
wherein a process performance index Cpk (Cpk) for the vial throughout a fill cycle exceeds a minimum value.
2. The method of claim 1, wherein setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees comprises setting the drip retraction parameter for the pump to one of 10 degrees, 20 degrees, or any value in a range of 10 degrees to 20 degrees.
3. The method of either of claims 1 or 2, further comprising setting an end drip retraction value to 290 degrees when setting the drip retraction parameter to 20 degrees or setting an end drip retraction value to 280 degrees when setting the drip retraction parameter to 10 degrees.
4. The method of any one of the previous claims, wherein providing a pump corresponding to a vial comprises providing a pump corresponding to a vial of a nested syringe and vial line.
5. The method of any one of the previous claims, wherein providing a pump corresponding to a vial comprises providing one or more of a first fill set or a second fill set, the first fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 2.0mm, and the second fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 3.0mm.
6. The method of any one of the previous claims, wherein a Cpk for the vial exceeds a minimum value throughout a fill cycle comprises one or more of: (1) the Cpk for the vial exceeds a value of 1.33; or (2) the Cpk for the vial exceeds the minimum value during a temperature range throughout the fill cycle, the temperature range one of: (1) 5 (+/-3) degrees Celsius; (2) 20 (+/-5) degrees Celsius; or (3) 10 to 19 degrees Celsius.
7. The method of any one of the previous claims, further comprising filling the vial with a drug product via the pump, wherein the drug product has one or more of the following characteristics: (a) a density in a range of about 1.0–1.2 g/cm³; (b) a viscosity in a range of about 1.0–10.0 cP; and (c) a surface tension in a range of about 40.0–72.7 mN/m.
8. The method of claim 7, wherein the drug product has a density in a range of about 1.0–1.2 g/cm³; a viscosity in a range of about 1.0–10.0 cP; and a surface tension in a range of about 40.0–72.7 mN/m.
9. The method of claim 7 or 8, wherein the drug product comprises a small molecule drug or a biologic drug.
10. A method of filling a plurality of vials of a nested syringe and vial line, the method comprising:
providing a plurality of pumps corresponding to a plurality of vials of a nested syringe and vial line;
setting a drip retraction parameter for each pump in the plurality of pumps to any value equal to or less than 20 degrees; and
filling each vial of the plurality of vials with a drug product via a corresponding pump of the plurality of pumps; and
wherein a process performance index (Cpk) for each vial of the plurality of vials throughout a fill cycle exceeds a minimum value.
11. The method of claim 10, further comprising setting a no adjustment limit for a fill weight of each vial to T1, with T1 being at or in a range of about 2% more or less than a fill weight of a target fill weight T0.
12. The method of either one of claims 10 or 11, wherein setting a drip retraction parameter for each pump to any value equal to or less than 20 degrees comprises setting the drip retraction parameter for the pump to one of 10 degrees, 20 degrees, or any value in a range of 10 degrees to 20 degrees.

13. The method of any one of claims 10-12, further comprising setting an end drip retraction value to 290 degrees when setting the drip retraction parameter to 20 degrees or setting an end drip retraction value to 280 degrees when setting the drip retraction parameter to 10 degrees.
14. The method of any one of claims 10-13, wherein filling each vial of the plurality of vials with a drug product via a corresponding pump of the plurality of pumps comprises filling each vial of the plurality of vials with a mAb formulation drug product.
15. The method of any one of claims 10-14, wherein a Cpk for each vial of the plurality of vials exceeds a minimum value throughout a fill cycle comprises one or more of: (1) the Cpk exceeds a value of 1.33; or (2) the Cpk for each vial of the plurality of vials exceeds the minimum value during a temperature range throughout the fill cycle, the temperature range one of: (1) 5 (+/-3) degrees Celsius; (2) 20 (+/-5) degrees Celsius; or (3) 10 to 19 degrees Celsius.
16. The method of any one of claims 10-15, wherein filling each vial with a drug product via a corresponding pump of the plurality of pumps comprises filling each vial with a drug product via the pump, wherein the drug product has one or more of the following characteristics: (1) a density in a range of about 1.0-1.2 g/cm³; (2) a viscosity in a range of about 1.0-10.0 cP; and/or (3) a surface tension in a range of about 40.0-72.7 mN/m.
17. The method of claim 16, wherein the drug product has a density in a range of about 1.0-1.2 g/cm³; a viscosity in a range of about 1.0-10.0 cP; and a surface tension in a range of about 40.0-72.7 mN/m.
18. The method of claim 16 or 17, wherein the drug product comprises a biologic drug or a small molecule drug.
19. A method of optimizing a filling recipe for a nested syringe and vial line, the method comprising:
 setting a drip retraction parameter for at least one pump in an offline manufacturing system corresponding to at least one container to any value equal to or less than 20 degrees;
 monitoring a performance of the at least one pump with the drip retraction parameter of the at least one pump set to any value equal to or less than 20 degrees;
 obtaining at least a minimum value for a process performance index (Cpk) for the at least one container throughout at least one fill cycle and for at least one drug product using the at least one pump in the offline manufacturing system; and
 finalizing a filling recipe for a nested syringe and vial line using data from fill cycles of the at least one drug product using the at least one pump in the offline manufacturing system.
20. The method of claim 19, further comprising monitoring a performance of the filling recipe in the nested syringe and vial line and obtaining at least a minimum value for the Cpk for the at least one container for each pump in a plurality of pumps in the nested syringe and vial line.
21. The method of claim 19, wherein setting a drip retraction parameter for at least one pump in an offline manufacturing system corresponding to at least one container to any value equal to or less than 20 degrees comprises setting the drip retraction parameter for a first fill set including a pump and a second fill set including a pump, each of the first and second fill sets in the offline manufacturing system, each of the first fill set and the second fill set having a corresponding filling container.
22. The method of any one of claims 19-21, wherein obtaining at least a minimum value for a Cpk for the container throughout at least one fill cycle and for at least one drug product comprises obtaining at least a minimum value for the Cpk of 1.33 for each container during a temperature of one or more of 5 (+/-3) degrees Celsius, 20 (+/-5) degrees Celsius, or any value in a range of 10 degrees to 20 degrees Celsius throughout a fill cycle, the minimum value for the Cpk being 1.33 for each container.
23. The method of any one of claims 19-22, wherein obtaining at least a minimum value for a Cpk for the container throughout a fill cycle and for at least one drug product comprises obtaining at least a minimum value for a Cpk for the container throughout at least one fill cycle and for the at least one drug product, the at least one drug product including one or more of: (1)

a mAb formulation; or (2) a drug product having one or more of: (a) a density in a range of about 1.0-1.2 g/cm³; (b) a viscosity in a range of about 1.0-10.0 cP; and (c) a surface tension in a range of about 40.0-72.7 mN/m.

24. The method of any one of claims 19-23, after setting the drip retraction parameter for the at least one pump in the offline manufacturing system, further comprising filling the at least one container with a drug product via the at least one pump, wherein filling the container with a drug product via the at least one pump comprises filling the container with a drug product including one or more of: (1) a mAb formulation; or (2) a drug product having one or more of: (a) a density in a range of about 1.0-1.2 g/cm³; (b) a viscosity in a range of about 1.0-10.0 cP; and (c) a surface tension in a range of about 40.0-72.7 mN/m.

25. The method of any one of claims 19-24, further comprising setting a no adjustment limit for a fill weight of the container to T1, with T1 being at or in a range of about 2% more or less than a fill weight of a target fill weight T0 after setting the drip retraction parameter.

26. The method of any one of claims 19-25, further comprising one or more of: setting a start pump dosing to 40 degrees, setting a pump dosing start ramp to 90 degrees, setting a pump dosing stop ramp to 210 degrees, setting an end pump dosing to 260 degrees, setting an end drip retraction parameter to 290 degrees, and setting a distance run per dose parameter to 766 degrees.

27. A method of filling a vial, the method comprising:
providing a pump corresponding to a vial;
setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees; and
setting a no adjustment limit for a fill weight of the vial to any value within a range of a target fill weight T0 and T1, with T1 being at or in a range between the target fill weight T0 and T2,

wherein a minimum value for a process performance index Cpk (Cpk) for the vial throughout a fill cycle is exceeded.

28. The method of claim 27, wherein setting a drip retraction parameter for the pump to any value equal to or less than 20 degrees comprises setting the drip retraction parameter for the pump to one of 10 degrees, 20 degrees, or any value in a range of 10 degrees to 20 degrees.

29. The method of either claim 27 or 28, further comprising setting an end drip retraction value to 290 degrees when setting the drip retraction parameter to 20 degrees or setting an end drip retraction value to 280 degrees when setting the drip retraction parameter to 10 degrees.

30. The method of any one of claims 27-29, wherein providing a pump corresponding to a vial comprises providing a pump corresponding to a vial of a nested syringe and vial line.

31. The method of any one of claims 27-30, wherein providing a pump corresponding to a vial comprises providing one or more of a first fill set or a second fill set, the first fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 2.0mm, and the second fill set including a peristaltic pump filling assembly having a needle with an outer diameter of about 3.0mm.

32. The method of any one of claims 27-31, wherein a Cpk for the vial exceeds a minimum value throughout a fill cycle comprises one or more of: (1) the Cpk for the vial exceeds a value of 1.33; or (2) the Cpk for the vial exceeds the minimum value during a temperature range throughout the fill cycle, the temperature range one of: (1) 5 (+/-3) degrees Celsius; (2) 20 (+/-5) degrees Celsius; or (3) 10 to 19 degrees Celsius.

33. The method of any one of claims 27-32, further comprising filling the vial with a drug product via the pump, wherein filling the vial with a drug product via the pump comprises filling the vial with a drug product including one or more of: (1) a density in a range of about 1.0-1.2 g/cm³; and/or (2) a viscosity in a range of about 1.0-10.0 cP; and/or (3) a surface tension in a range of about 40.0-72.7 mN/m.