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Method and system for producing sterile solution filled containers

Abstract

A cartridge assembly for a filling machine includes a plurality of containers. Each container includes a volume and a stem connected to the volume. A connection line grid is in fluid communication with each stem of the plurality of containers. The connection line grid includes a first row connected to one or more containers of the plurality of containers and a second row connected to one or more containers of the plurality of containers. A filter assembly is coupled to the connection line grid.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application a national phase of International Application No. PCT/US21/64494, filed Dec. 21, 2021, and entitled “METHOD AND SYSTEM FOR PRODUCING STERILE SOLUTION FILLED CONTAINERS,” which claims the benefit of U.S. Provisional Application No. 63/130,979, filed Dec. 28, 2020, and entitled “METHOD AND SYSTEM FOR PRODUCING STERILE SOLUTION FILLED CONTAINERS,” the entireties of which are expressly incorporated by reference herein.

FIELD OF DISCLOSURE
(1) The present disclosure relates to sterile solution-filled containers, and more particularly, to a method, system, and machine for producing sterile solution-filled containers.
BACKGROUND
(2) Conventional methods for manufacturing bags of sterile solution include filling bags in a clean environment with a solution, sealing the filled bag of solution, and then sterilizing the fluid and bags in a sterilizing autoclave. This can be referred to as terminal sterilization. Another conventional method is to sterile-filter a solution and to fill and seal sterile bags in an extremely high-quality environment designed and controlled to prevent contamination of the solution during the filling process and to seal the filled bag. This can be referred to as an aseptic filling process.
(3) The terminal sterilization process generally requires one or more autoclaves to produce the sterilizing heat and steam needed to suitably sterilize the bag of solution for medical use. These autoclaves generally are not economical unless they can produce large batches of terminally sterilized bags. Typically, centralized manufacturing facilities can afford the capital expenditure needed and space requirements to produce and ship sterile solution-filled bags. In addition to these costs, the application of terminal sterilization processes may degrade the solution formulation contained in the bags, thereby leading to incompatible or unstable formulations. Moreover, terminal sterilization does not eliminate non-viable contamination.
(4) The aseptic manufacturing process must occur in a sterile working environment, and requires expensive equipment, stringent procedures and extensive monitoring to ensure that solution product bags meet certain environmental and manufacturing regulatory standards. Sterilizing a working environment, by itself, can be costly and time consuming. Additional precautions apply

for technicians involved in the filling process to ensure the production of safe and sterile products. Even with these safeguards, unless it can be verified that the solution entering the bag is sterile, there is a risk that contaminants may have inadvertently been introduced into the solution during filling/sealing. Once introduced, unless the solution later passes through a viable sterilizing filter, the contaminants will remain in the solution.

SUMMARY

(5) In accordance with a first exemplary aspect, a method for producing sterile solution-filled containers may include positioning a cartridge onto a filling machine. The cartridge may include a plurality of containers, a filter assembly, a connection line in fluid communication with the filter assembly, and a reservoir coupled to the connection line, disposed upstream from the plurality of containers, and disposed downstream from the filter assembly. Each of the plurality of containers may include a volume and a stem having a first end in fluid communication with the volume and a second end in fluid communication with the connection line. The method may include coupling the cartridge to a feed line in fluid communication with a fluid source, and activating a pump coupled to the feed line. The method may include at least partially filling one or more of the volumes associated with the plurality of containers by pumping fluid through the feed line, the filter assembly, the reservoir, and the connection line, thereby creating one or more at least partially filled containers. After filling, the method may include sealing the stem of each of the at least partially filled containers at a location between the connection line and the volume of the at least partially filled containers, thereby creating one or more at least partially filled and sealed containers. Finally, the method may include separating each of the at least partially filled and sealed containers from the connection line while maintaining at least a portion of the seal on the stem.

(6) In accordance with a second exemplary aspect, a cartridge assembly for a filling machine may include a plurality of containers. Each container may include a volume and a stem connected to the volume. A connection line grid may be in fluid communication with each stem of the plurality of containers. The connection line grid may include a first row connected to one or more containers of the plurality of containers and a second row connected to one or more containers of the plurality of containers. A filter assembly may be coupled to the connection line grid.

(7) In accordance with a third exemplary aspect, a machine for producing a plurality of solution-filled containers may include a seal and cut assembly including a sealer, a cutter, and a carriage carrying the sealer and the cutter. The seal and cut assembly may be movable in a lateral direction and in a longitudinal direction. A bracket may receive a cartridge of containers. The machine may include a first group of pinch valves that include a first column and a second column spaced from the first column. A second group of pinch valves may be disposed between the first column and the second column. The second group of pinch valves may be movable in the longitudinal direction.

(8) In further accordance with any one or more of the foregoing first, second, or third exemplary aspects, a method, system, and machine for producing sterile solution containers may further include any one or more of the following preferred forms.

(9) In a preferred form, which may be combined with any other form, or portion thereof, the method may include at least partially filling the reservoir with a solution from the mix tank before at least partially filling one or more volumes.

(10) In a preferred form, which may be combined with any other form, or portion thereof, the method may include activating a second pump coupled to the connection line.

(11) In a preferred form, which may be combined with any other form, or portion thereof, the second pump may be disposed downstream from the reservoir and upstream from the plurality of containers.

(12) In a preferred form, which may be combined with any other form, or portion thereof, the method may include reversing the second pump after separating each of the at least partially filled and sealed containers from the connection line.

(13) In a preferred form, which may be combined with any other form, or portion thereof, at least partially filling one or more of the volumes may include filling a first row of the connection line with a solution.
(14) In a preferred form, which may be combined with any other form, or portion thereof, the first row may include one or more containers.
(15) In a preferred form, which may be combined with any other form, or portion thereof, filling a first bag of the first row may include releasing a first valve coupled to the connection line of the first row.
(16) In a preferred form, which may be combined with any other form, or portion thereof, filling the first bag of the first row may include releasing a second valve coupled to a stem of the first bag.
(17) In a preferred form, which may be combined with any other form, or portion thereof, the method may include filling a second bag of the first row after opening a third valve coupled to a stem of the second bag.
(18) In a preferred form, which may be combined with any other form, or portion thereof, the method may include closing the second valve coupled to the stem of the first bag.
(19) In a preferred form, which may be combined with any other form, or portion thereof, the method may include moving a seal and cut assembly in a lateral direction from the first bag of the first row to the second bag of the first row.
(20) In a preferred form, which may be combined with any other form, or portion thereof, at least partially filling one or more of the volumes may include filling a second row of the connection line with a solution after separating each of the at least partially filled and sealed containers from the first row of the connection line.
(21) In a preferred form, which may be combined with any other form, or portion thereof, the second row may be parallel to the first row and may include one or more containers.
(22) In a preferred form, which may be combined with any other form, or portion thereof, the method may include moving a seal and cut assembly in a longitudinal direction from the first row toward the second row of the connection line before filling a second row of the connection line.
(23) In a preferred form, which may be combined with any other form, or portion thereof, the method may include purging air from the feed line before at least partially filling the one or more volumes.
(24) In a preferred form, which may be combined with any other form, or portion thereof, the method may include purging air from the connection line of the cartridge before at least partially filling the one or more volumes.
(25) In a preferred form, which may be combined with any other form, or portion thereof, purging air from the connection line may include activating a second pump to deliver air from the connection line to a reservoir disposed above the connection line.
(26) In a preferred form, which may be combined with any other form, or portion thereof, purging air from the connection line may include purging a first row of the connection line by opening a first row supply valve and opening a first row return valve.
(27) In a preferred form, which may be combined with any other form, or portion thereof, the first row may include a first end, a second end, and one or more containers disposed between the first and second ends.
(28) In a preferred form, which may be combined with any other form, or portion thereof, the first end may be coupled to the first row supply valve and the second end may be coupled to the first row return valve.
(29) In a preferred form, which may be combined with any other form, or portion thereof, the method may include decoupling the cartridge from the filling machine and coupling a different cartridge to the filling machine.
(30) In a preferred form, which may be combined with any other form, or portion thereof, the different cartridge may include a plurality of containers, a filter assembly, and a connection line in

fluid communication with the filter assembly.
(31) In a preferred form, which may be combined with any other form, or portion thereof, each of the plurality of containers of the different cartridge may include a volume and a stem having a first end in fluid communication with the volume and a second end in fluid communication with the connection line.
(32) In a preferred form, which may be combined with any other form, or portion thereof, sealing the stem may include capturing the stem with a sealing device and collecting sealing sensor data associated with a seal of the stem.
(33) In a preferred form, which may be combined with any other form, or portion thereof, the at least one sensor is associated with a sealing energy source, such as an RF generator.
(34) In a preferred form, which may be combined with any other form, or portion thereof, sealing the stem may include analyzing, by one or more processors of a controller, the sensor data associated with the seal.
(35) In a preferred form, which may be combined with any other form, or portion thereof, sealing the stem may include identifying, by one or more processors, based on an analysis of the sensor data, a status or condition associated with the seal.
(36) In a preferred form, which may be combined with any other form, or portion thereof, the method may include accepting the seal if an average weld power, analyzed by the one or more processors, is within a stored acceptable weld power range.
(37) In a preferred form, which may be combined with any other form, or portion thereof, the method may include rejecting the seal if an average weld power, analyzed by the one or more processors, is less than a lower limit of a stored acceptable weld power range.
(38) In a preferred form, which may be combined with any other form, or portion thereof, the method may include rejecting the seal if a direct short is detected in the sealing device by the one or more processors.
(39) In a preferred form, which may be combined with any other form, or portion thereof, the method may include rejecting the seal if an average weld power, analyzed by the one or more processors, is greater than an upper limit of a stored acceptable weld power range or less than a lower limit of the stored acceptable power range.
(40) In a preferred form, which may be combined with any other form, or portion thereof, the method may include re-sealing the stem.
(41) In a preferred form, which may be combined with any other form, or portion thereof, the filter assembly may include a first filter and a second filter arranged in series.
(42) In a preferred form, which may be combined with any other form, or portion thereof, a reservoir may be coupled to the connection line grid.
(43) In a preferred form, which may be combined with any other form, or portion thereof, the reservoir may be disposed upstream from the plurality of containers.
(44) In a preferred form, which may be combined with any other form, or portion thereof, the reservoir may be disposed downstream from the filter assembly.
(45) In a preferred form, which may be combined with any other form, or portion thereof, the reservoir may include a volume, an inlet port, and an outlet port.
(46) In a preferred form, which may be combined with any other form, or portion thereof, the reservoir may be disposed above, with respect to gravity, the connection line grid.
(47) In a preferred form, which may be combined with any other form, or portion thereof, the connection line grid may include a network of interconnected tubing defining a supply manifold, a return manifold, the first row, and the second row.
(48) In a preferred form, which may be combined with any other form, or portion thereof, the first row and the second row may extend between the supply manifold and the return manifold.
(49) In a preferred form, which may be combined with any other form, or portion thereof, the supply manifold of the connection line grid may be coupled to the outlet port of the reservoir.

(50) In a preferred form, which may be combined with any other form, or portion thereof, the return manifold may be coupled to the inlet port of the reservoir.
(51) In a preferred form, which may be combined with any other form, or portion thereof, the network of interconnected tubing may include at least one rigid portion connected to at least one flexible portion.
(52) In a preferred form, which may be combined with any other form, or portion thereof, each of the first and second rows may include a first end, a second end, and a fill manifold connecting the first and second ends.
(53) In a preferred form, which may be combined with any other form, or portion thereof, the first and second ends may be flexible and the fill manifold may be rigid.
(54) In a preferred form, which may be combined with any other form, or portion thereof, the supply manifold may be coupled to the first end of each of the first and second rows.
(55) In a preferred form, which may be combined with any other form, or portion thereof, the return manifold may be coupled to the second end of each of the first and second rows.
(56) In a preferred form, which may be combined with any other form, or portion thereof, the fill manifold of each of the first and second rows may include one or more ports corresponding to the one or more containers of each of the first and second rows.
(57) In a preferred form, which may be combined with any other form, or portion thereof, each port corresponding to one container may be in fluid communication with one stem.
(58) In a preferred form, which may be combined with any other form, or portion thereof, each row of the first and second rows of the connection line grid may be coupled to at least two of the plurality of containers.
(59) In a preferred form, which may be combined with any other form, or portion thereof, the seal and cut assembly may include at least one sensor and a controller.
(60) In a preferred form, which may be combined with any other form, or portion thereof, the controller may include one or more processors.
(61) In a preferred form, which may be combined with any other form, or portion thereof, the controller may include a memory communicatively coupled to the one or more processors and storing executable instructions that, when executed by the one or more processors, causes the one or more processors to receive data captured by the at least one sensor, analyze the data to identify a status or condition associated with a seal created by the sealer, and send a signal to a controller of the machine to accept or reject the seal.
(62) In a preferred form, which may be combined with any other form, or portion thereof, a conveyor may be disposed below, relative to gravity, the seal and cut assembly.
(63) In a preferred form, which may be combined with any other form, or portion thereof, the conveyor may be movable with the seal and cut assembly.
(64) In a preferred form, which may be combined with any other form, or portion thereof, the bracket for the cartridge may be coupled to a plurality of rails.
(65) In a preferred form, which may be combined with any other form, or portion thereof, the bracket and the plurality of rails may be configured to remove or receive a cartridge of containers.
(66) In a preferred form, which may be combined with any other form, or portion thereof, the one or more containers may be one or more containers.
(67) In a preferred form, which may be combined with any other form, or portion thereof, the one or more containers may be one or more vials.
(68) In a preferred form, which may be combined with any other form, or portion thereof, the one or more containers may be one or more syringes.
(69) In a preferred form, which may be combined with any other form, or portion thereof, positioning a cartridge onto a filling machine may include positioning a cartridge having a plurality of containers as containers, each product bag including a bladder as the volume.
(70) In a preferred form, which may be combined with any other form, or portion thereof,

positioning a cartridge onto a filling machine may include positioning a cartridge having a plurality of vials as containers.
(71) In a preferred form, which may be combined with any other form, or portion thereof, positioning a cartridge onto a filling machine may include positioning a cartridge having a plurality of syringes as containers.
(72) In a preferred form, which may be combined with any other form, or portion thereof, the one or more containers may include one or more containers, and wherein the volume is a bladder.
(73) In a preferred form, which may be combined with any other form, or portion thereof, the plurality of containers may include a plurality of containers, and wherein the volume is a bladder.
(74) In a preferred form, which may be combined with any other form, or portion thereof, the plurality of containers may include a plurality of vials.
(75) In a preferred form, which may be combined with any other form, or portion thereof, the plurality of containers may include a plurality of syringes.

Description

BRIEF DESCRIPTION OF THE DRAWINGS
(1) FIG. **1** is a schematic diagram of an exemplary system for producing sterile solution containers in accordance with the teachings of the present disclosure;
(2) FIG. **2** is a perspective view of a first exemplary cartridge of the system of FIG. **1** assembled in accordance with the teachings of the present disclosure;
(3) FIG. **3** is a perspective view of an exemplary row isolated from the cartridge of FIG. **2**;
(4) FIG. **4** is a perspective view of an exemplary group of containers isolated from the cartridge of FIG. **2**;
(5) FIG. **5** is a perspective view of a different exemplary cartridge with three groups of containers assembled in accordance with the teachings of the present disclosure;
(6) FIG. **6**A is a perspective view of a second exemplary cartridge that may be used with the system of FIG. **1**, and is assembled in accordance with the teachings of the present disclosure;
(7) FIG. **6**B is a top view of the cartridge of FIG. **6**A;
(8) FIG. **6**C is a side view of the cartridge of FIG. **6**A;
(9) FIG. **7** is a perspective view of a third exemplary cartridge that may be used with the system of FIG. **1**, and is assembled in accordance with the teachings of the present disclosure;
(10) FIG. **8** is a perspective view of a fourth exemplary cartridge that may be used with the system of FIG. **1**, and is assembled in accordance with the teachings of the present disclosure;
(11) FIG. **9** is a schematic diagram of the system of FIG. **1** during a phase of the filling process showing wetting a filter assembly and filling a reservoir of a cartridge;
(12) FIG. **10** is a schematic diagram of the system of FIG. **1** showing a purge phase of the supply and return manifolds of the cartridge;
(13) FIG. **11** is a schematic diagram of the system of FIG. **1** showing a purge phase of a fill manifold of a first row of the cartridge;
(14) FIG. **12** is a schematic diagram of the system of FIG. **1** showing a filling phase of a first bag of the first row of the cartridge;
(15) FIG. **13** is a schematic diagram of the system of FIG. **1** showing a filling phase of a second bag of the first row of the cartridge with the first filled bag sealed and removed from the cartridge;
(16) FIG. **14** is a schematic diagram of the system of FIG. **1** showing a purge phase of a fill manifold of a second row of the cartridge;
(17) FIG. **15** is a schematic diagram of the system of FIG. **1** showing a filling phase of a first bag of the second row of the cartridge;
(18) FIG. **16** is a schematic diagram of the system of FIG. **1** showing a filling phase of a second

bag of the second row of the cartridge with the first filled bag sealed and removed from the cartridge;
(19) FIG. **17** is a schematic diagram of the system of FIG. **1** showing a solution recapture phase after all of the containers of the cartridge have been filled, sealed, and removed from the cartridge;
(20) FIG. **18**A is a side view of a filling machine used in the system of FIG. **1**, and is assembled in accordance with the teachings of the present disclosure;
(21) FIG. **18**B is a front view of the filling machine of FIG. **18**A;
(22) FIG. **18**C is a back view of the filling machine of FIG. **18**A;
(23) FIG. **18**D is a top view of the filling machine of FIG. **18**A;
(24) FIG. **19** is a perspective view of a tray assembly for use with the filling machine of FIGS. **18**A-**18**D;
(25) FIG. **20** is a perspective view of a gantry system of the filling machine of FIGS. **18**A-**18**D, holding the tray assembly of FIG. **19**;
(26) FIG. **21** is a front perspective view of a seal and cut assembly of the filling machine of FIGS. **18**A-**18**D;
(27) FIG. **22** is a back perspective view of the seal and cut assembly of FIG. **21**;
(28) FIG. **23** is a flow diagram of a first exemplary method of filling a plurality of containers with sterile solution in accordance with the teachings of the present disclosure;
(29) FIG. **24** is a flow diagram of a second exemplary method of filling a plurality of containers with sterile solution in accordance with the teachings of the present disclosure; and
(30) FIG. **25** is an exemplary system of a plurality of cartridges connected to a single filter assembly assembled in accordance with the teachings of the present disclosure.

DETAILED DESCRIPTION

(31) The present disclosure relates to a flexible filling platform that may be used for sterile filling multiple containers with solution without the need for specialized barrier systems, such as, for example, isolators and closed restrictive access barrier systems (RABS). The disclosed filling platform includes a filling system, a disposable cartridge of containers, and a filling machine to increase filling capacity and efficiency, ensure sterility and safety of the end product, and automate production.
(32) In FIG. **1**, a schematic diagram of a system **10** for filling a plurality of containers with a sterile solution is illustrated in accordance with the teachings of the present disclosure. The system **10** includes a fluid source, which may be a mix tank **14**, a feed line **18**, and a cartridge **22**. A solution mixed in the mix tank **14** is delivered to a plurality of containers, and in this example product bags **26**, of the cartridge **22** by passing the solution through an endotoxin-removing batch filter **30**, a filter assembly **34** of the cartridge **22**, and reservoir, which may be an intermediate container **38**, of the cartridge **22** before the solution is pumped from the reservoir **38** and into each of the plurality of bags **26**. In other examples, the fluid source **14** of the system **10** may have in-line mixing in combination or instead of a mix tank. The feed line **18** and a connection line **46** of the cartridge **22** are in fluid communication with each other to permit the flow of the solution from the mix tank **14** and into the connection line **46** to fill the plurality of bags **26** of the cartridge **22**. The feed line **18** and the connection line **46** are connected at an aseptic cartridge connector **50**. First and second pumps **42**, **44** and isolation valves coupled to the feed line **18** and connection line **46** of the cartridge **22** to pump and control, respectively, the flow of solution through the system **10**. Specifically, the dual pump configuration separates the pumping operation: the first pump **42** draws fluid from the mix tank **14** for delivery to the cartridge **22**, and the second pump **44** accurately pumps fluid within the cartridge **22**. In an alternative arrangement, the first pump **42** may also be replaced with a mix tank pressurizing system using pressurized filtered air or nitrogen to transfer solution to the reservoir **38**.
(33) FIG. **2** illustrates an exemplary cartridge **22** of the system **10** of FIG. **1**. The cartridge **22** includes the plurality of containers **26**, the filter assembly **34**, the reservoir **38**, and the connection

line **46**. The plurality of containers **26** may be one of a variety of product bags **26**, an in a preferred example, each bag **26** is the same size and includes a volume **52** and a stem **54** connected to the volume **52**. The connection line **46** is a network of interconnected tubes and includes a solution distribution grid **56** in fluid communication with each stem **54** of the plurality of containers **26**. The solution distribution grid **56** includes a supply manifold **58**, a return manifold **62**, and a plurality of rows **66** connecting the supply manifold **58** and return manifold **62**. The connection line **46** includes a plurality of connected rigid portions to reduce lag and to provide structure, and a plurality of flexible portions to allow for fluid isolation at various locations and stages or phases of the filling cycle.

(34) Non-limiting examples of acceptable containers for the plurality of containers **26** of the cartridge **22** are disclosed in U.S. Pat. No. 10,617,603, U.S. Patent Publication No. 2020/0214938, U.S. Patent Publication No. 2020/0222281, U.S. Patent Publication No. 2020/0146932, U.S. Patent Publication No. 2020/0147251, U.S. Patent Publication No. 2020/0146931, and U.S. Patent Publication No. 2020/0147310, the entire contents of each of which are expressly incorporated herein by reference. While the containers **26** are illustrated in the figures as product bags **26** with bladders **52**, the containers may include syringes, vials, bottles, or other vessels having bladders, reservoirs, or internal volumes for holding a solution.

(35) An exemplary row **66** of the solution distribution grid **56** of the first exemplary cartridge **22** is shown in more detail in FIG. **3**. The row **66** includes a first end **70**, a second end **74**, a fill manifold **78** connecting the first and second ends **70**, **74**, and ten product bags **26** in fluid communication with the fill manifold **78**. The fill manifold **78** includes a plurality of ports where each port is connected to the stem **54** of each bag **26**. The first and second ends **70**, **74** of the row **66** are made of flexible tubing, such as, for example, flexible PVC tubing, whereas the fill manifold **78** is made of a rigid tubing, such as, for example, PVC. The row **66** includes a supply connector **82** and a return connector **86** that connect to the supply and return manifolds **58**, **62**, respectively, of the grid **56**. In particular, the supply connectors **82** of the row **66** connect together to form a continuous supply manifold **58**, and the return connectors **86** of the row **66** connect together to form a continuous return manifold **62**. The supply and return connectors **82**, **86** are T-shaped and made of a rigid plastic, such as a PVC.

(36) FIG. **4** illustrates an exemplary group of bags **67** of the first exemplary cartridge **22**. The group **67** includes a plurality of rows **66** connected together via the connectors **82**, **86** to form the supply and return manifolds **58**, **62**. The group **67** is a modular unit having first and second open ends **71**, **73** that may be connected to a final row **156**, another group **67**, or the supply and return lines **106**, **110** of the cartridge **22**. For example, in FIG. **5** the cartridge **22** includes three connected groups **67**A, **67**B, **67**C. The first group **67**A is connected to the supply and return lines **110**, **1106**, and to the second group **67**B of bags. The second group **67**B is connected to the supply and return manifolds **58**, **62** of the first and third groups **67**A, **67**C, and the third group **67**C is connected to the second group **67**B and a final row **156** to complete a closed cartridge. The modular arrangement of the group **67** of bags enables filling more bags per filtration assembly **34**. As shown in FIG. **5**, the supply and return manifolds **58**, **62** of each group **67** are connected to provide a cartridge **22** with 270 bags.

(37) While the schematic cartridge **22** of FIG. **1** includes four rows **66** of eight product bags **26**, and the exemplary cartridge **22** of FIG. **2** includes nine rows **66** of ten product bags **26**, other exemplary cartridges **22** may include more or fewer rows **66** with more or fewer product bags **26**. In fact, cartridge size may be determined based on capacity of a gamma radiation carrier used for sterilizing each cartridge prior to use. The cartridge of FIG. **5** includes three groups **67**A, **67**B, and **67**C, but may be arranged to connect with additional groups **67**. The group **67** of FIG. **4** is sized in order to maximize the number of bags per cartridge that may be gamma sterilized at one time. However, in other examples, the number of rows **66** and number of bags **26** per row **66** may vary.

(38) As shown in FIGS. **1** and **2**, the reservoir **38** is coupled to the solution distribution grid **56**,

disposed upstream from the plurality of bags **26** and the second pump **44**, and disposed downstream from the filter assembly **34**. In this example, the reservoir **38** is a flexible bag **38**, but may be a different type of container that can maintain the solution in a sterile environment. The reservoir **38**, which may be an intermediate bag, includes a volume or bladder **90**, an inlet port **94**, an outlet port **98**, and a solution recovery port **168** and is coupled to the grid **56** of the cartridge **22** to supply the plurality of bags **26** with sterile solution. Because the reservoir **38** is disposed between the filter assembly **34** and the second pump **44**, the second pump **44** draws filtered solution from the bladder **90** of the reservoir **38** to fill the remainder of the connection line **46** (downstream from the reservoir **38**) and supply the solution distribution grid **56** with sterile solution.

(39) Generally speaking, the reservoir **38** is coupled to the grid **56** by connections at the inlet and outlet ports **94**, **98**, thereby forming a complete loop. The inlet port **94** of the reservoir **38** is connected to a T-connector **102** that receives both (1) a solution filtered through the filter assembly **34**, and (2) a solution from a return line **106** of the grid **56**. The outlet port **98** of the reservoir **38** is coupled to a supply line **110**, which provides a solution pathway to the supply manifold **58**. The supply line **110** includes a peristaltic tubing portion **114** for operatively coupling the connection line **46** to the second pump **44**, which may be a peristaltic pump. The closed loop forms by connecting the outlet port **98** to the supply line **110**, which is connected to the supply manifold **58** that is coupled to the return manifold **62**, and connecting the return line **106**, which is coupled to the return manifold **62**, to the inlet port **94**. So configured, the supply manifold **58** fluidly connects the first end **70** of each row **66** to the outlet port **98** of the reservoir **38**, and the return manifold **62** fluidly connects the second end **74** of each row **66** to the inlet port **94** of the reservoir **38**. Additionally, and as will be described below, the return manifold **62** also provides a solution return path during various cycles while running the system **10** to deliver purged air as well as unused solution from the grid **56** and to the reservoir **38**.

(40) Solution pumped from the mix tank **14** must first pass through the filter assembly **34** before reaching the reservoir **38**. The filter assembly **34** of the cartridge **22** includes a first filter **118** and a second filter **122** arranged in series. Each filter **118**, **122** is a sterilizing grade filter, and may be selected based on compatibility with the solution, sterilizing technology, and required fill rate. As shown in FIG. **2**, each filter **118**, **122** is coupled to a sample bag **126**, **130**, respectively. The sample bags **126**, **130** are used to receive purged air and solution samples. The sample bag **126** receives a sample of pre-filter solution, and sample bag **130** receives a solution sample after the first filter **118** and before the second filter **122**. The sample bag **130** also receives purged air from filter **118**. Purged air from the second filter **122** is collected in the reservoir **38**. The solution from sample bag **130** is tested in lab for any growth to determine its effectiveness. The first and last filled bags **26** from the cartridge **22** are tested for testing effectiveness of the filter assembly **34**. The filter assembly **34** lasts for the duration of the fill (i.e., the entire cartridge **22**) with a stable flow rate and ability to filter out any bioburden. However, if there are any deficiencies in the performance of either the first or second filters **118**, **122**, an operator may be able to detect such issues by analyzing the filters via a filter integrity test at the end of a cartridge fill, and testing the contents of the sample bags **130** and the first and last filled bags **26** from the cartridge **22** for any particulate matter or bio contamination. At the end of the filling cycle, the filter assembly **34** is discarded with the remainder of the single-use cartridge **22**. The used filter cartridge **22** is tested for leaks with a vacuum leak detector. Any leaks detected in the cartridge **22** trigger an automatic hold on the bags **26** filled. In another example, the used filter cartridge **22** may be tested for flaws using integrity testing methods.

(41) The cartridge **22** is pre-assembled in a clean room (ISO 7/ISO8) and gamma sterilized prior to being connected to the solution supply system (i.e., the mix tank **14** and feed line **18**) to ensure that all surfaces that come into contact with the filtered solution are sterile. The solution distribution grid **56** is primarily designed for “single use.” However, the cartridge **22** may be adapted for

multiple uses depending on assembly components, component materials, safety, and sterilization methodology. The solution distribution grid **56** is designed to (1) ensure that the solution is directed to a targeted product bag **26** without any risk of contamination; (2) isolate the product bags **26** not being filled; (3) enable removal of any trapped air in the grid **56** prior to filling the product bags **26**; and (4) provide direct flow paths to all product bags **26** in the grid **56** to fill the bags **26** with a high level of accuracy and repeatability without the need for fill pump recalibration.

(42) FIGS. **6**A, **6**B, and **6**C illustrate a second exemplary cartridge **222** that may be used with the system **10** of FIG. **1** to provide a plurality of sterile solution-filled product bags. The second exemplary cartridge **222** is similar to the first exemplary cartridge **22** of FIGS. **1-3**. Thus, for ease of reference, and to the extent possible, the same or similar components of the cartridge **222** will retain the same reference numbers as outlined above with respect to the first exemplary cartridge **22**, although the reference numbers will be increased by 200 and will include an “A” or a “B” where appropriate. However, the second cartridge **222** differs from the first exemplary cartridge **22** by providing one filter assembly **234** coupled to two different solution distribution grids **256**A, **256**B.

(43) As shown in FIG. **6**A, the filter assembly **234** includes a first filter **318** and a second filter **322** disposed in series and coupled to a first reservoir **238**A of the first solution distribution grid **256**A and a second reservoir **238**B of the second solution distribution grid **256**B. So configured, the cartridge **222** is coupled to the feed line **18** of the system **10** of FIG. **1** at the cartridge connector **50**. Just as the reservoir **38** of the first exemplary cartridge **22** is filled with solution, the first and second reservoirs **238**A, **238**B of the second exemplary cartridge **222** are also filled with a sterile solution. The two sterilizing grade filters **318**, **322** sterilize enough solution to fill twice as many product bags as the single cartridge **22**. As shown in FIG. **6**A, a main connection line **246** coupled to the filter assembly **234** splits into a first connection line **246**A and a second connection line **246**B, where each connection line **246**A, **246**B connects to a T-connector **302**A, **302**B of each respective grid **256**A, **256**B. In another example, multiple individual cartridges may be assembled to a single filter train with additional connectors (FIG. **25**).

(44) Other cartridge configurations are possible, and may be designed specifically to address the needs of the system **10** or various environmental or budgetary constraints. For example, the placement of a cartridge connector **50** may vary to enhance versatility of cartridge configurations. For example, a different example cartridge **422** in FIG. **7** includes an aseptic cartridge connector **450** adjacent to a single filter **522** of a filter assembly for connecting to a mating connector **50** in the feedline **18**. In yet another example in FIG. **8**, an example cartridge **822** has an aseptic cartridge connector **850** disposed downstream of a filter assembly. This configuration reduces production costs for larger batches. By comparison to the filters **118**, **122** of the cartridges **22** of FIGS. **2** and **5**, the filters upstream from the cartridge **422**, **822** are not discarded after filling, and may be used for a whole batch (e.g., more than 2000 bags). After filling, a new cartridge **422**, **822** is connected to the filter line. The other components of the cartridges **422**, **822** of FIGS. **7** and **8** are otherwise the same or substantially similar to the components of the cartridge **22** of FIG. **2**. The aseptic cartridge connector may be an AseptikQuike Sterile Connector.

(45) Returning to FIG. **1**, the system **10** includes a plurality of isolation valves to control the flow of solution through the feed line **18**, connection line **46**, supply line **110**, supply manifold **58**, return manifold **62**, return line **106**, each fill manifold **78**, and each stem **54** of the plurality of bags **26**. These valves are positioned adjacent to a flexible portion of tubing of the system **10** to isolate, pinch, engage, or otherwise close the flexible tubing to prevent solution from flowing through the flexible tubing, or open, release, or otherwise disengage from the flexible tubing to allow solution to flow through the valve and continue through the system **10**. A first valve **165** is a main system isolation valve and is operated (e.g., open/close, release/pinch or engage) to control a solution supply from the mix tank **14** to the cartridge **22**. A main feed valve **134** is always closed after the first pump **42** has been turned off to ensure that there is no back pressure or reverse flow through

the filter. A third valve **138** is a supply valve and is located downstream from the reservoir **38** and upstream from the second pump **44**. The supply valve **138** is operated to distribute solution from the reservoir **38** and into the solution distribution grid **56**. A fourth valve **142** is a return valve located on the return line **106** to control a return of either purged air or unused solution from the grid **56** into the reservoir **38**.

(46) Additionally, the system **10** includes two groups of isolation valves operated to control the flow of solution through each row **66** of bags **26**. The first group of isolation valves includes a first column of supply manifold valves **146** (which may include one or more valves, depending on the number of rows **66** of the cartridge **22**) and a second column of return manifold valves **150**. The first and second columns **146**, **150** are pinch valves and are arranged according to the number of rows and layout of the grid **56**. Specifically, the first and second columns **146**, **150** are arranged near the first ends **70** and second ends **74**, respectively, of the rows **66**. However, in other examples, these isolation valves may be a different type of valve and may be arranged in a different configuration according to the layout of the solution distribution grid **56**. A supply manifold valve **152** and a return manifold valve **154** are coupled to a final row **156** of the grid **56**. The final row **156** does not include any fill ports connected to product bags **26**, but instead the final row **156** connects the supply and return manifolds **58**, **62** to complete the loop of the grid **56** to purge the grid **56** of either air or solution, depending on the phase of the filling cycle.

(47) A second group of valves **160** are fill valves and are disposed between the first column and the second column of valves **146**, **150**. The fill valves **160**, which may also be pinch valves, are operated to control the flow of solution from the fill manifold **78** into each bladder **52** of the plurality of bags **26**. The fill valves **160** are positioned so that each valve **160** is adjacent to the flexible tubing of one stem **54** of the plurality of bags **26**. As shown in FIG. **1**, the fill valves **160** are adjacent to the stems **54** of the plurality of bags **26** of the first row **66**. As will be discussed below, the fill valves **160** are movable relative to the cartridge **22** to engage the stems **54** of the plurality of bags **26** of each additional row **66**. However, in another exemplary arrangement, the system **10** may include further sets of valves **160** corresponding with the number of rows **66** in the cartridge **22** so that there is a pinch valve for each stem **54** of the cartridge **22**.

(48) Turning now to FIGS. **9-17**, a fill cycle of the system **10** will be illustrated and described in different phases of the filling cycle. Initially, the feed line **18** is purged of any trapped air by running the first pump **42**. As solution is drawn from the mix tank **14** and into the feed line **18**, any air in the feed line **18** is pushed through a vent **164**, which is disposed downstream from the first pump **42** and upstream from the main isolation valve **165**. While the feed line **18** is purged and air vented through the vent **164**, the main system isolation valve **165** closes, thereby isolating the entire cartridge **22** and the filter assembly **34** from the feed line **18**.

(49) After the air is purged from the feed line **18**, the main system isolation valve **165** opens, the supply valve **138** and the return valve **142** close, and the first pump **42** pumps solution from the mix tank **14** to wet the filter assembly **34** of the cartridge **22** to fill the reservoir **38** with a desired amount of solution. As shown in FIG. **9**, the portion of the cartridge **22** downstream from the reservoir **38** is isolated to allow the filter assembly **34** to be properly wetted and for the reservoir **38** to fill with enough solution to purge the supply and return manifolds **58**, **62** and a first fill manifold **78** of the cartridge **22** before filling the bags **26**. The first pump **42** runs at a pace to sufficiently wet the filters without overwhelming the system **10**. The sample bag **126** of the filter assembly **34** may be later analyzed to confirm suitable performance of the first filter **118** in the filter assembly **34**. If the first filter **118** is compromised, the additional filter **122** of the two-filter filter assembly **34** ensures that the solution is sufficiently sterile upon passing to the reservoir **38**.

(50) In the next phase of the filling cycle shown in FIG. **10**, the portion of the cartridge **22** downstream from the reservoir **38** opens to ready the system **10** for purging the cartridge **22** of trapped air and then filling the bags **26** with solution. In this phase, the supply valve **138** and the return valve **142** coupled to the outlet and inlet ports **98**, **94** of the reservoir **38**, respectively, open.

Additionally, the supply manifold valve **152** and return manifold valve **154** coupled to the final row **156** of the solution distribution grid **56** open as well. The fill manifold **78** of each row **66** (not including the final row **156**) is isolated as each supply manifold valve **146** and return manifold valve **150** closes (not including the supply and return manifold valves **152**, **154** of the final row **156**). The second pump **44** runs to purge the air trapped in the supply and return manifolds **58**, **62** from the solution distribution grid **56**. As indicated by the arrows in FIG. **10**, solution from the reservoir **38** pushes the air through the outlet port **98**, supply line **110**, the supply manifold **58**, the final row **156**, the return manifold **62**, the return line **106**, and into the inlet port **94** of the reservoir **38**. The reservoir **38**, which is disposed at least partially above the solution distribution grid **56** (with respect to gravity), receives and traps the purged air in the headspace of the reservoir **38**. This configuration facilitates air management by advantageously using the buoyancy of the air to push the solution (coming in from below the air, or headspace, of the bag) to ensure accurate filling volumes. As the air is purged from the supply and return manifolds **58**, **62**, sterile solution fills the outer perimeter of the grid **56**.

(51) In FIG. **11**, a first row **66**A of the grid **56** is purged of air trapped in the fill manifold **78**A. To purge the air, a first supply manifold valve **146**A and a first return manifold valve **150**A on opposite ends of the row **66**A open, and the supply and return manifold valves **152**, **154** of the final row **156** close. Valves **146** and **150** from other rows **66** remain closed. The second group of valves **160** remain closed to isolate the plurality of bags **26**. As shown by the arrows, air trapped in the grid **56** is purged only from the first row **66**A.

(52) FIG. **12** illustrates a first bag **26**A of the first row **66**A being filled. To fill the bags **26** of the first row **66**, the supply manifold valve **146**A of the first row **66**A remains open, the return manifold valve **150**A of the first row **66**A closes, and solution fills the fill manifold **78**A of the first row **66**A. A first fill valve **160**A opens to allow solution to flow through the stem **54** and into the bladder **52** of the first bag **26**A. The second pump **44** meters the required solution into the first bag **26**A to avoid under-filling or overfilling each bag **26** during the fill cycle. Once the first bag **26**A is filled, the first fill valve **160**A closes around the stem **54** of the first bag **26**A and a second fill valve **160**B of an adjacent second product bag **26**B opens. While the second bag **26**B is filled, the stem **54** of the first bag **26**A is sealed at a location between the bladder **52** and the fill manifold **78**, and specifically below the first fill valve **160**A. After an adequate seal is made, the first bag **26**A is separated from the fill manifold **78**A of the cartridge **22**, as shown in FIG. **13**.

(53) This process is repeated for the remaining bags **26** of the first row **66**A until each bag **26** is filled, sealed, and separated from the grid **56**. As will be described below, a seal and cut assembly of a filling machine may automatically seal and cut each stem **54** once each bag **26** is filled. The filling machine automates the filling cycle by communicating with the fill valves **160** and with the seal and cut assembly so that before each bag **26** is cut from the grid **56**, the bag **26** is filled with the required volume of solution, the fill valve **160** closes around the stem **54**, and a suitable seal is formed on the stem **54**.

(54) The seal and cut assembly is configured to move in a lateral direction parallel to the row **66** to consecutively seal and cut each stem **54** of the plurality of bags **26** in the row **66**. Filling, sealing, and cutting may occur simultaneously on different bags **26** of the same row. For example, when a third bag **26** is being filled, a sealing device of the seal and cut assembly may seal the stem **54** of a second filled bag **26** while a cutting device of the seal and cut assembly cuts the stem **54** at the seal of the first filled bag **26**. Each filled, sealed, and cut bag **26** is separated from the cartridge **22** and is received by a chute and/or a conveyor belt disposed below the grid **56**. After the last bag **26** is sealed and removed from the row **66**, the seal and cut assembly returns to an initial position (i.e., adjacent to where the first bag **26**A was hanging before being separated from the grid **56**) and moves toward a second row **66**B of the cartridge **22**.

(55) In the next phase shown in FIG. **14**, the bags **26** of the first row **66**A are separated from the grid **56**, and the fill valves **160** engage the stems **54** of the bags **26** of a second row **66**B. The first

supply and return manifold valves **146**A, **150**A close, and second supply and return manifold valves **146**B, **150**B coupled to the second row **66**B open. The second pump **44** pumps solution from the reservoir **38**, through the supply line **110** and a portion of the supply manifold **62**, and into a second fill manifold **78**B. Consequently, any trapped air in the second fill manifold **78**B of the second row **66**B is purged through the return line **106** and into the inlet port **94** of the reservoir **38**. In FIG. **15**, the return manifold valve **150**B of the second row **66**B closes, the supply manifold valve **146**B stays open, and the first fill valve **160**A opens to allow solution to fill the first bag **26**C of the second row **66**B. In FIG. **16**, the first bag **26**C of the second row **66**B is sealed and removed from the grid **56** while a second bag **26**D of the second row **66**B is filled. The phase of filling, sealing, and cutting is repeated for each remaining bag **26** of the second row **66**B until each bag **26** is filled, sealed, and removed from the grid **56**. Again, the seal and cut assembly of the machine indexes to a position adjacent to a first bag of the following row **66**.

(56) Finally, in a last phase of the filling cycle shown in FIG. **17**, each bag **26** from the cartridge **22** has been removed and the stems **54** have been sealed to isolate the fill ports of the fill manifolds **78**. The supply valve **138**, the supply manifold valves **146**A-D, **152**, and the return manifold valves **150**A-D, **154** open, the return valve **142** closes, and the second pump **44** reverses to pull any solution disposed in the grid **56** and deliver the remaining solution through the supply line **110** and into the reservoir **38** through the outlet port **98**. The inlet and outlet ports **94**, **98** of the reservoir **38** are sealed, and the reservoir **38** is removed from the cartridge **22**. A third port **168** of the reservoir **38** may then be connected to the mix tank **14** to transfer the recovered solution back into the mix tank **14**.

(57) In summary, the reservoir **38** provides a plurality of roles in the filling cycle of the system **10**. First, the reservoir **38** serves as an intermediate bag or volume of solution downstream of the filters **118**, **122** for collecting solution used during the wetting stage of the filters **118**, **122** of the filter assembly **34**. The solution used for wetting the filters **118**, **122** in this phase is collected, rather than wasted, and used for filling the product bags **26**. Second, the reservoir **38** serves as a volume for trapped air that is purged from the system **10** in the purge phases. As previously mentioned, the reservoir **38** is disposed above the grid **56**, thereby receiving the trapped air in its headspace. Third, the reservoir **38** serves as an intermediate solution source for filling the bags **26**. Instead of directly drawing from the filter assembly **34**, the second pump **44** only draws sterile solution from the reservoir **38**. This ensures that filling can be carried out at the desired flow rate without increasing the pressure drop across the filter assembly **34**, thereby protecting the integrity of the filters **118**, **122**. This configuration also helps improve fill accuracy by isolating the second pump **44** from the inherent variability introduced by the filters **118**, **122** during its use cycle (as filter pores progressively clog up, the pressure drop for a given flow rate through the filter starts to change which would otherwise negatively impact the fill accuracy of the metering pump positioned upstream relative to the filters **118**, **122**). Fourth, the reservoir **38** serves to minimize waste of the system **10** by receiving any unused solution (i.e., not delivered to a product bag **26**) from the distribution grid **56**. After all the solution is pulled back into the reservoir **38**, the supply and return ports **94**, **98** of the bag **38** are sealed and the bag **38** is disconnected from the distribution grid **56**. Using the third port **168** of the reservoir **38**, the contents of the reservoir **38** can be returned back to the mix tank **14** safely and without any contamination risk. Finally, and as will be described in more detail below, the amount of solution in the reservoir **38** is monitored closely for active fill management. This is achieved by mounting the reservoir **38** on a load cell, which monitors the exact amount of solution in the reservoir **38** at any time during the fill cycle. Towards the end of the bag fill phase, the control system of the machine actively manages the amount of solution in the reservoir **38** to ensure that reservoir **38** is almost empty when the cycle ends.

(58) The exemplary system **10** and method of producing sterile solution-filled product bags **26** may be used with a machine, such as the machine **400** in FIGS. **18**A-**18**D. The machine **400** automates many phases of the filling cycle described above by including a programmable logic controller

("PLC") **402**, the seal and cut assembly **404**, a sealing controller **408**, a sealing energy (e.g., an RF generator) **490**, a load cell **412** communicatively coupled to the first and second pumps **42**, **44**, a gantry system **416**, the supply and return manifold valves **146**, **150**, and the fill valves **160**. The machine **400** also includes a user interface **420** to display various commands, messages, and status updates, and to operate the PLC **402** of the machine **400**. The machine **400** of FIGS. **18**A-**18**D is capable of simultaneously processing two separate cartridges **22**, and therefore includes a set of each of the components necessary to process the cartridges (e.g., seal and cut assemblies, pumps, gantry systems, isolation valves, etc.). However, for the sake of simplicity, one set of the machine components will be labeled in the figures. Therefore, it may be presumed that the components of a left side of the machine **400** is identical, and a mirror image of the labeled components of the right side of the machine (as depicted in FIG. **18**A).

(59) The on-board PLC **402** of the machine **400** operates and controls various components of the system **10** during the filling process and is configured to interact with an operator by displaying commands, communicating results, providing status updates, and alerting the operator to system or performance errors via the user interface **420**. Generally, the PLC **402** includes one or more processors and a memory coupled to the one or more processors and that stores executable instructions for running the fill cycle. The PLC **402** is configured to receive signals from proximity switches and other sensors, transmit commands or signals to actuating devices of the system **10** (e.g., the pumps **42**, **44**, the seal and cut assembly **404**, the first and second groups of valves **146**, **150**, **160**), monitor sensors (e.g., the load cell **412**, a sensor in a sealing device), and process information gathered and received from the sensors.

(60) For example, the PLC **402** communicates with a first pump **42** to begin pumping a solution from the mix tank **14** to wet the filter assembly **34**, as shown and described above with respect to FIG. **9**. The PLC **402** also communicates with the load cell **412** to determine the amount of solution being pumped into the reservoir **38** and subsequently each individual bag **26** of the cartridge **22** as a secondary check. The PLC **402** communicates with the second pump **44** to stop pumping the solution when each of the product bags **26** has been filled to a desired capacity. Additionally, the PLC **402** signals to the second pump **44** to reverse after all the bags **26** have been filled, sealed, and separated from the grid **56**, as shown in FIG. **17**. Further, the PLC **402** is configured to communicate with each isolation valve **165**, **134**, **138**, **142**, **146**, **150**, **152**, **154**, **160** (i.e., to open or close) during each phase of the filling cycle **500**. In the illustrated example, the PLC **402** controls the operation of the machine **400** locally (e.g., a wired connection) and may be accessed by the user interface **420** of the machine **400**. In other embodiments, the PLC **402** may remotely control the operation of the machine **400** via wireless communication systems. Each of the RF generator **490**, load cell **412**, and peristaltic pumps **42**, **44** includes a controller. The PLC communicates with each of the controllers to set up process parameters, send instructions, and receive process data.

(61) The PLC **402** may be programmed to store data for each batch of viable product bags **26** that have been filled and tested for sterility. Before filling, an operator may enter a serial number associated with the cartridge **22** into the PLC **402** via the user interface **420** to store type of solution, solution expiration, filling date and location, fluid conductivity and integrity results, and other information pertaining to the product bags **26**. In other examples, each batch of filled product bags **26** may be serialized by other means with or without the use of the PLC **402**. For example, the bags **26** may be labeled before or after the bags **26** are filled. If both filters **118**, **122** of the cartridge **22** fail, then each of the corresponding bags **26** may be segregated out for discard.

(62) The seal and cut assembly **404**, shown in FIGS. **18**D, **21**, and **22**, includes the sealing controller **408**, the sealing energy (e.g., an RF generator) **490**, a sealer **424**, a cutter **428**, a conveyor **432** (not illustrated in FIGS. **21** and **22**) disposed below the sealer **424** and cutter **428**, one or more sensors, and a carriage **436** carrying the sealer **424** and cutter **428**. The seal and cut assembly **404** is servo-controlled using linear transfer units **433**, **434** to move in directions parallel to respective X and Y axes of the machine **400**. For example, the X-direction linear transfer unit **433** moves the two

carriages **436** of the two seal and cut assemblies **404** in the X-direction. The linear transfer unit **433** includes two independently driven linear drive units. Each carriage **436** is coupled to only one linear drive unit, but uses the guide rail of the other linear drive unit for support via a floating linear bearing mounted on the guide rail of the other linear drive unit. Thus, each of the two seal and cut heads may be driven independently and may also adequately support the two sealing control units **408** attached to the two seal and cut assemblies **404**. The linear transfer unit **434** moves the two seal and cut assemblies **404** and the two valve assemblies **160** in the Y-direction. In one example, the transfer unit **434** includes of two linear drive units coupled via a coupling shaft connected to a single servo motor.

(63) To seal and cut each stem **54** of the plurality of bags **26** of a row **66**, the carriage **436** moves the sealer **424** and the cutter **428** along the X axis. The carriage **436** moves to programmed positions to align the sealer **424** and cutter **428** with the stems **54** of the plurality of bags **26**. The sealer **424** and the cutter **428** are spaced from each other the same or similar distance between adjacent stems **54** in a given row **66**. In this way, the sealer **424** is in position to seal one stem **54** and the cutter **428** is in position to cut the adjacent sealed stem **54**. After a seal and a cut have been made, the carriage **436** moves the sealer **424** and cutter **428** to the next position to seal and cut the stems **54** until all bags **26** of one row **66** are removed from the cartridge **22**. After the last bag **26** of the row **66** has been cut from the cartridge **22**, the seal and cut assembly **404** and valves **160** mounted on the transfer unit **434** move along or parallel to the Y axis

(64) In some examples, a chute may be disposed below the sealer **424** and cutter **428** to direct bags **26** separated from the cartridge **22** onto the conveyor **432**. The chute is coupled to the seal and cut unit whereas the conveyor **432** is mounted directly to the linear transfer unit **433**. As a seal and cut assembly **404** positions itself for a bag **26**, the chute is in the correct position to direct the separated bag **26** onto the conveyor **432**. When the linear transfer unit **433**, carrying the seal and cut assemblies **404** and the valves **160**, advances to a row, the conveyor **432** advances with it and therefore is positioned correctly to receive bags separated from the cartridge **22**.

(65) Separately, the sealer **424** and the cutter **428** are also pneumatically controlled to move relative to the carriage **436** when performing their respective seal and cut functions. For example, after a bag **26** is filled and the fill valve **160** engages the stem **54**, the sealer **424** extends in the Y direction, away from the carriage **436**, to engage the stem **54** and create a seal. After a seal is determined to be satisfactory, which is described in more detail below, the sealer **424** retracts back to the carriage **436**. The carriage then indexes in the X direction and the sealer **424** again extends in the Y direction to seal a second stem **54**, and the cutter **428** extends in the Y direction, away from the carriage **436**, to cut the first sealed stem **54**. After the cutter **428** cuts the first stem **54** and the sealer **424** seals the second stem **54**, both the sealer **424** and the cutter **428** return back to the carriage **436** before the carriage **436** moves again in the X direction to process the next bag **26**. In another example, however, the sealer **424** and cutter **428** do not engage different stems **54** of adjacent bags **26** simultaneously. Rather, the sealer **424** extends to seal one stem **54**, retracts after the stem **54** is adequately sealed, and then the carriage **436** advances to position the cutter **428** in front of the stem **54** before the cutter **428** extends to cut the stem **54**.

(66) To make a seal, the sealer **424** of the seal and cut assembly **404** extends toward the stem **54** of the bag **26** in an open position and clamps onto the stem **54** once in place. The sealing tool **424** is connected to a radiofrequency (“RF”) generator by way of the controller **408**. The sealer emits RF energy between opposing clamped surfaces to heat the polymer of the stem **54**, causing the stem **54** to melt sufficiently, bond, and form a seal. The sealing tool **424** forms a sufficiently wide seal to allow adequate welded length on each end after bag **26** has been cut away. The sealed portion of the tube is cut into two sections where the upper section remains with the cartridge **22** and the lower section becomes part of the bag **26**. The width of the seal may depend on the properties of the tubing of the stem **54** to ensure that the seal withstands a squeeze test on the bag for at least ten seconds at 20 psi. The cutter **428** is arranged to cut at or near a midpoint of the width of the seal to

create two sealed ends (i.e., a sealed end of the stem **54** connected to the bag **26** and a sealed end of the upper section of the stem **54** remaining with the cartridge **22**) so that the cartridge **22** is maintained in a closed state.

(67) The sealing tool **424** is electrically coupled to the sealing controller **408**, which in turn is linked to the RF generator **490** associated with the sealer **424**. The RF generator is in communication with the PLC **402** so that the PLC **402** of the machine **400** can control and/or monitor the adequacy of the seal. The sensors of the seal and cut assembly **404** are arranged to measure incident and reflected power. The sealing controller **408** controls delivery of the power to the sealing jaws during the weld cycle to prevent over seals or under seals. A memory linked to the PLC **402** stores executable instructions that, when executed by the PLC **402**, causes the one or more processors to receive data captured by the RF generator and analyze the data to identify a status or a condition associated with the seal created by the sealer **424** to signal the machine **400** to accept or reject the seal. The sealing controller **408** can sense a direct short and the RF generator **490** can sense amount of incident (forward) energy and the reflected energy during sealing.

(68) Prior to running the machine **400**, the PLC **402** may be set up to establish an acceptable average weld power range (i.e., average power over the duration of the weld) for the fill tube weld. During the sealing operation, the PLC **402** compares real-time weld data captured by the RF generator with the acceptable average weld power range stored in the memory. Based on this comparison, the PLC **402** makes one of the following determinations of (1) accepting the seal, (2) rejecting the seal, or (3) signaling to the sealing tool **424** to re-seal the stem **54**. For example, the seal is accepted when an average weld power is within the stored acceptable weld range, or the seal is rejected when the average weld power is less than a lower limit of the acceptable average weld range or if a short circuit is detected in the clamp of the sealer **424**.

(69) If captured average weld power is less than the lower limit of the acceptable average weld range, the machine **400** will automatically attempt a re-seal provided the maximum number of sealing attempts has not been reached. Specifically, the PLC **402** makes such a determination and communicates with the sealing tool **424** so that the filling cycle does not continue until the stem **54** is re-sealed. If the captured average weld power is greater than the upper limit of the acceptable weld power range, it indicates an over-seal. In this example, the clamp of the sealer **424** is kept closed around the stem **54** and the operator is instructed to manually seal the stem **54** and remove the bag **26** from the cartridge **22**. The machine **400** is equipped with a second manual hand-held sealer and cutter in addition to the primary automated sealer **424**. If a short is detected at the sealing clamp, the sealing controller **408** immediately cuts off power to the sealing clamp and the sealing clamp remains in the closed position. The machine **400** then prompts the operator to manually seal and remove the bag **26**. When a seal is rejected, the machine **400** advances to the next bag **26** in the cartridge **22** only after the remedial steps have been completed successfully. Sealing data for every bag **26** is recorded and stored in a secure database and is reported for the purposes of batch release.

(70) The PLC **402** also communicates with the load cell **412** to monitor the amount of solution running through the system **10** for filling the plurality of bags **26** to avoid unnecessary waste. As previously mentioned, the reservoir **38** is mounted on the load cell **412**, which monitors the exact amount of solution in the reservoir **38** at any time during the fill cycle. At different phases of the fill cycle, the load cell **412** will communicate with the PLC **402** and the first pump **42** to add more solution to the reservoir **38**. Towards the end of the fill cycle, the PLC **402** actively manages the amount of solution in the reservoir **38** to ensure that reservoir **38** is almost empty when the cartridge **22** is completely filled. After all bags **26** of the cartridge **22** have been filled, the PLC **402** registers the weight input from the load cell **412** before reversing the direction of the second pump **44** to recover the solution from the filled cartridge, as described in connection with FIG. **17**. After the end of the recovery cycle, the PLC **402** again registers the weight of the reservoir **38**. The weight of the recovered solution is calculated from the initial and final weights of the reservoir **38** measured by PLC **402**, which then uses the data to compare with the historical average. A lower-

than-average recovered weight may indicate a leak in cartridge **22**.

(71) The gantry system **416** is a movable gripper configured to receive and position a cartridge **22** relative to the machine **400** for the filling cycle. In FIG. **19**, a tray **417** carrying a cartridge **22** is illustrated. The tray **417** is a support structure that secures the cartridge **22** to the gantry system **416**, and includes a frame **419** supporting the grid **56** of the cartridge **22** and a rotatable swing arm **421**. In the illustrated example, the frame **419** includes slots or grooves shaped to hold each row **66** of the cartridge. In FIG. **19**, the swing arm **421** is in a closed position and is disposed on top of the tubing of each row **66**, thereby clamping the cartridge **22** to the tray **417**. In FIG. **20**, the tray capture mechanism of the gantry system **416** is illustrated holding the tray **417** and cartridge **22** of FIG. **19**. The gantry system **416** securely receives and couples to the tray **417**, and positions the supply end **58** and return end **62** of each row **66** with the corresponding supply and return manifold valves **146**, **150**. In FIG. **18**D, the gantry system **416** is configured to receive the tray **417** from the end of the machine **400** and position the tray **417** adjacent to the seal and cut assembly **404**.

(72) As previously discussed, the supply and manifold valves **146**, **150** form two columns, where each column is adjacent to an opposite end of each row **66** of the cartridge **22**. The supply and manifold valves **146**, **150** are suspended from a top rack **460** of the machine **400** by suspension rods **464**. When the cartridge **22** is loaded to the machine **400**, the cartridge **22** is not necessarily in proper position for interacting with the isolation valves **146**, **150**, **160**. Therefore, to set up the cartridge **22** in the proper place for the filling cycle, the gantry system **416** moves the cartridge **22** in a direction parallel to the Z axis to meet the stationary isolation valves **146**, **150**, **160** of the machine **402**.

(73) The illustrated exemplary machine **400** is a fully automated machine with automated loading and unloading of cartridges **22**, filling, sealing, and cutting. However, other mechanisms and arrangements of the machine **400** may be used to carry out each phase of the machine cycle. For example, the movement of the gantry system **416** may be facilitated by an operator by sliding the gantry system **416** into place along the rails **458** of the machine **400** and into position. In yet another example, the seal and cut operations of each bag **26** may be semi-automated or completely manual. Other sealing technologies may also be used, such as, for example, thermal heat transfer, ultrasonic welding, or other suitable methods based on the material of the tube **54**.

(74) Turning now to FIG. **24**, a method **600** of filling a plurality of product bags **26** using the machine **400** is described with respect to a multi-cartridge batch of FIG. **25** and with reference to the fill operation steps described in FIGS. **9-17**. FIG. **25** is a schematic diagram of an example system **610** for filling a plurality of containers of the multi-cartridge batch with a sterile solution. The system **610** is similar to the system **10** of FIG. **1** described above, with similar reference numbers (although increased by 600) for similar components, but includes a different filter assembly **634** and cartridge arrangement. It will be appreciated that the system **610** of FIG. **25** operates in a slightly different manner than the system **10** of FIG. **1**.

(75) The system **610** of FIG. **25** is arranged to deliver a solution from a solution source, for example a mix tank **614**, to a plurality of containers through a filter assembly **634** and into the multi-cartridge connection and solution distribution grid **611**. An aseptic connector **651** of a feed line **618** is arranged to connect to a corresponding aseptic connector **653** coupled to the filter assembly **634**. The endotoxin filter **630** is connected upstream of the first fill pump **642** in the feedline **618**. The filter assembly **634** includes a first sterilizing grade filter **619** and a final sterilizing grade filter **622**. Each filter **619**, **622** is coupled to a sample bag **726**, **730**, respectively. The sample bags **726**, **730** are used to receive purged air disposed in the feedline **618** and filter **619**. Additionally, the sample bag **726** may receive solution from the feedline **618**, and the sample bag **730** may receive solution passing through the first filter **619**, which can be monitored to ensure suitable performance and/or tested to determine the effectiveness of the filter **619**. The first and last filled bags from the cartridge are tested to verify effectiveness of the second filter **622**.

(76) Unlike the first system **10**, the system **610** includes the multi-cartridge connection and solution

distribution grid **611** providing a manifold **613** downstream from the filter assembly **634** with several aseptic connectors arranged to aseptically connect to one or more cartridges **622**A, **622**B. The solution distribution grid **611** and filter set **634** are part of the same assembly and are sterilized together. In the illustrated example, the manifold **613** includes twenty separate lines **615**, which may be flexible silicon tubing, arranged to connect the manifold **613** to twenty different aseptic connectors **650**, which may be, for example, AseptikQuik® Sterile Connector. The filter set **634** includes two filters **619**, **622** (e.g., both sterilizing grade filters) and the manifold **613** containing several male/female/genderless ends of aseptic connectors **650**A, **650**B. The other male/female/genderless aseptic connector ends **650**A-A-**650** B-B are attached to each one of the cartridges **622**A, **622**B that need to be filled. In the schematic, only two cartridges **622**A, **622**B are illustrated. A first connector **650**A is arranged to connect a first connection line **646**A to the first cartridge **622**A, for example, and a second connector **650**B is arranged to connect a second connection line **646**B to the second cartridge **622**B. However, the solution distribution grid **611** may include an aseptic connector for every cartridge that requires filling in a batch.

(77) In the illustrated example, one or more pinch valves may be arranged to clamp on the manifold lines **613** to control fluid flow into the cartridges **622**A, **622**B. For example, a pinch valve adjacent to the line **615**A may be open to permit fluid to flow from the manifold **613** and into the first line **615**A to begin filling the first cartridge **622**A. Meanwhile, a pinch valve adjacent to the line **615**B may be closed to prevent fluid from flowing into the second cartridge **622**B. At an end of the manifold **613**, opposite the filter assembly **634**, a reservoir **619** is in fluid communication with the manifold **613** to receive purged air from the manifold **613**. In other examples, the manifold **613** may be arranged to have more or fewer connectors **650** than illustrated, and/or may be arranged so that only a fraction of the twenty connectors **650** are coupled to cartridges **622**A, **622**B, as shown in FIG. **25**.

(78) Similar to the first system **10**, a first pump **642** is coupled to the feed line **618** to pump solution from the fluid source **614** through the feed line **618** and into the filter assembly **634**. Each cartridge **622**A, **622**B coupled to the manifold **613** is separately coupled to a second pump (e.g., a peristaltic pump) arranged to interact with a tubing portion **714**A, **714**B of each respective supply line **710**A, **710**B. The multi-pump configuration separates the pumping operation of the system **710**: the first pump **642** draws fluid from the mix tank **614** for delivery to the manifold **613**, and the second pump accurately pumps fluid from a reservoir **638**A, **638**B into the containers **626**A, **626**B of each cartridge **622**A, **622**B.

(79) The machine **400** assures production of sterile solution-filled product bags **626** by performing a plurality of steps of the method **600**. In this method **600**, the filter set **634** is loaded in the machine **400** separately from the cartridges **622**A, **622**B. After both the cartridges **622**A, **622**B and the filter set **634** are loaded, the operator connects the two ends of the aseptic connectors **650**, one first end connected to the manifold **613** and the other end connected to the cartridge **622**. Once connected the filling operation proceeds as described previously. At the end of filling and after solution recovery, the connecting line **646** is sealed and then cut into two sections, one section remaining with the used aseptic connector on the filter set **634** and the other section remaining with the used cartridge **622**. The used cartridge is removed and replaced with a new cartridge but the filter set **634** remains on the machine. When a new cartridge **622** is loaded, the aseptic connector end of the cartridge **622** is connected with one of the unused aseptic connectors from the filter set connector manifold. This ensures a sterile fill for all cartridges **622**.

(80) For the first two cartridges in a batch **622**A and **622**B, after the aseptic connector ends **650**A and **650**A-A and connector ends **650**B and **650**B-B are connected, the filling cycle begins, as previously described, by activating the first pump **642** to purge the feed line **618**. The main isolation valve **765** closes and air is vented through vent **764**. Next, the main isolation valve **765** opens to wet the filters **630**, **722** of the filter assembly **634**, and to fill the reservoirs **638**A and **638**B. Then, air trapped in each grid **656**A, **656**B is purged by closing a main feed valve **734**A,

734B, and opening a supply valve **738**A, **738**B (FIG. **25**), the supply manifold valve **152**, the return manifold valve **154**, and the return valve **142**, as shown in FIG. **10**. To fill the plurality of bags **626**A, **626**B in step **612**, multiple steps are performed by the machine **400** and step **612** is repeated for all rows **666** for each solution distribution grid **656**A, **656**B of the cartridges **622**A and **622**B. In other words, the method steps **620-636** are performed for each row **666**A, **666**B before advancing to the next row **666** and repeating the fill cycle of step **612**. For ease of reference, the steps performed on each grid **656**A, **656**B will be described with reference to the first exemplary cartridge **22** and system **10** of FIGS. **1**, **7-19**.

(81) In step **620**, trapped air from a first row **66**A is purged through the connection line **46** of the cartridge **22** before filling the first bladder **52** of bag **26**, as shown in FIG. **11**. When purging the first row **66**A of the connection line **46**, the machine **400** opens a first row supply manifold valve **146**A and a first row return manifold valve **150**A. Because the first end **70** of the supply manifold **78**A of the first row **66**A is coupled to the first row supply manifold valve **146**A and the second end **74** is coupled to the first row return manifold valve **150**A, air and solution may flow through the entire fill manifold **78**A of the first row **66**A. However, solution does not enter the bladders **52** of each bag **26** because the isolation valves **160** coupled to the stems **54** are closed. To purge air from the fill manifold of row **66**, a pre-validated volume of solution is pumped by the pump **44** through the fill manifold back to the reservoir **38** disposed at least partially above the connection line **46**. This pushes the air out from the fill manifold of row **66** into the reservoir **38**. The pump **44** communicates with the PLC **402** to close the return manifold valve **150**A of the first row **66**A in step **620**, as shown in FIG. **12**. This is repeated for each subsequent row **66** after all bags in the previous row have been filled sealed and removed by cutting. This is done by operating the supply and return manifold valves **146**, **150** corresponding to each row **66**.

(82) Immediately after closing the return manifold valve **150**A, the first fill valve **160**A coupled to the stem **54** of the first bag **26**A opens to allow solution into the bladder **52** of the first bag **26**A. The load cell **412** monitors the reservoir **638** to ensure there is enough volume in the reservoir **38** to begin the purging/filling process. The second pump **44** meters the desired volume of solution into each of the product bags **26**. As filling proceeds, the load cell **412** will control the first pump **42** transferring fluid from the mix tank **14** through the filter assembly **634** to the reservoir **638** so that there will be sufficient solution for the filling process to proceed. As the filling process is about to conclude, the load cell **412** aims for minimal remaining volume in the reservoir **638**.

(83) When the first bag **26**A is filled, the first fill valve **160**A closes to isolate the filled bladder **52** of the first bag **26**A. Shortly thereafter, step **628** is repeated for the second bag **26**B of the first row **66**A. Specifically, the second bag **26**B of the first row **66**A is filled after opening a fill valve **160**B coupled to a stem **54** of the second bag **26**B and closing the fill valve **160**A coupled to the stem **54** of the first bag **26**A. While the second bag **26**B is being filled, step **636** of sealing and cutting the first bag **26**A is performed and the first bag **26** is removed from the cartridge **22**, as shown in FIG. **13**.

(84) The step **636** of sealing and cutting the bag **26** in step **636** includes running a program of the one or more processors of the PLC **402**. The stored program is executed by the PLC **402** by instructing the seal and cut assembly **404** to seal the stem **54** of the first bag **26**A with the sealing device **424**. This includes moving the sealing device **424** towards the stem **54** and clamping the stem **54**, at a location beneath the fill valve **160**A and above the bladder **52**, to RF seal the stem **54**. The RF generator captures sealing power data associated with a seal of the stem **54**, and the one or more processors of the PLC **402** analyzes the power data (incident or forward power and the reflected power) associated with the seal. For example, the one or more processors of the PLC **402** compares the captured data with the stored data related to a good seal, and then identifies, based on an analysis of the data, a status or condition associated with the seal. The machine **404** will then either (1) accept the seal if an average weld power, analyzed by the one or more processors of the PLC **402**, is within a stored acceptable weld power range, (2) reject the seal if an average weld

power, analyzed by the one or more processors of the PLC **402**, is less than a lower limit of a stored acceptable weld power range; (3) reject the seal if a short circuit is detected in the sealer **424** by RF control **408**; or (4) reject the seal if the average weld power, analyzed by the one or more processors of the PLC **402**, is greater than an upper limit of a stored acceptable weld power range. If the seal is rejected, the PLC **402** signals to the sealing device **424** to re-seal the stem **54** provided the maximum number of validated re-seals allowed have not been exceeded. If the seal is accepted, then the sealing device **424** moves away from the stem **54** and the cutting tool **428** moves toward the seal and cuts the stem **54** at the seal into two sections to separate the bag **26**A from the fill manifold **78**A, as shown in FIG. **13**. This may include, as described above, moving the seal and cut assembly **404** in a lateral direction from the first bag **26**A of the first row **66**A to the second bag **26**B of the first row **66**A. However, if the seal is rejected (either after a re-seal or because of a short circuit), the PLC **402** will create an alert and display the error on the user interface **420**, instructing an operator to manually seal the stem **54** and cut the bag **26** from the cartridge **22**.

(85) Steps **628** and **632** of the method **600** are repeated to fill, seal, and cut each bag **26** from the first row **66**A. Step **640** of moving to the next row **66** is executed by indexing the seal and cut assembly **404** in the lateral direction (along the X axis of the machine **400**) to return to its initial position adjacent to the stem **54** of the first bag **26**A, and then in a longitudinal direction (along the Y axis of the machine **400**) from the first row **66**A toward a second row **66**B. After step **640** is complete, steps **620** and **624** are executed for the second row **66**B before steps **628**, **632**, and **636** are executed to fill, seal, and cut each bag **26** of the second row **66**B, as shown in FIGS. **14-16**. This cycle is repeated for each row **66** of the solution distribution grid **56** until all bags **26** are removed from the grid **56**, as shown in FIG. **17**. At this point, the PLC **402** instructs the second pump **44** to reverse, the return valve **142** to close, and the return and supply manifold valves **156**, **154**, **152**, **146** to open for purging the grid **56** of any remaining solution in the supply and return manifolds **58**, **62** and fill manifolds **78** of each row **66**. The solution is pushed into the reservoir **38**.

(86) Finally, step **644** includes decoupling the cartridge **622** from the filling machine **400** and coupling a different cartridge **622** to the filling machine **400** to repeat the filling cycle. The different cartridge being the same or similar than the previously filled cartridge, and the PLC **402** may be run on a different program depending on the size and number of bags **26** of the cartridge **622**. The filter set assembly **634** remains on the machine **400**.

(87) In the method **600**, after the last cartridge **622** in a given batch has been filled, to ensure sterility of the contents of the product bag **26**, the filter assembly **34** is sealed off and separated from the connection line **646** of the last cartridge **622** for testing in a filter integrity test machine or device. In case when the filter assembly **34** is integrated with the cartridge **22**, the filter assembly **34** is sealed and separated from the used cartridge(s) to check for filter integrity. Both filters **118**, **122** from the filter assembly **34** are tested to determine, with a high degree of certainty, that the solution of the filled product bags **26** is sufficiently sterile. Even if one of the filters **118**, **122** of the filter assembly **634** fails and the other does not, the solution in bags **26** will be sterile. It is also possible to test only one of the filters and test the other one only if the first one fails the filter integrity test.

(88) The filter testing device may be pre-programmed or controlled to perform a filter integrity test, such as a bubble test, a pressure degradation test, water intrusion test, a water flow test, or any suitable test known in the art. A pressure degradation test is a method for testing the quality of a filter either before or after the filter has been used. To perform the integrity test, a test head of the filter testing device engages the inlet of the filter assembly **34**. The filter integrity test determines the presence of any structural flaws in the filter membrane that may prevent the filter **118**, **122** from adequately sterilizing a solution. For example, a hole having a diameter larger than 0.2 microns (μm) in the filter membrane may allow particulates, viable or no-viable, in the fluid, to pass through the filter **118**, **122** and compromise or contaminate the sterile environment of the bladder.

(89) To perform the filter integrity test using a pressure degradation test procedure, the test head

engages the inlet of the filter **118**, **122** and applies an air pressure of a predetermined value to the inlet **65** and filter membrane. In one example, the predetermined value is the pressure where gas cannot permeate the membrane of an acceptable filter. A pressure sensor, or other method of measuring the integrity of the filter, is located within the test head and measures the pressure decay or diffusion rate through the filter membrane. The results from the integrity test are assessed to determine the quality of the filter **118**, **122**, and therefore the quality of the solution of the filled product bags **26**. If the pressure sensor measures a decay or an unexpected rate of decay, then the filter **118**, **122** fails the test.

(90) Alternatively, in a bubble point test, the test head gradually increases the pressure applied to the filter **118**, **122**, and the increase in pressure is measured in parallel with the diffusion rate of the gas through the filter media. Any disproportionate increase in diffusion rate in relation to the applied pressure may indicate a hole or other structural flaw in the filter membrane, and the filter **118**, **122** would fail the integrity test.

(91) In addition to filter integrity test for the filters, a vacuum leak test is performed on every used cartridge. The used cartridge is placed inside a chamber which is sealed before applying a vacuum to the chamber. The time required to generate a certain level of vacuum is measured. In case if the time required is greater than a pre-validated time or if the required validated vacuum pressure is not able to be reached, the cartridge is deemed to have failed the vacuum test. The used cartridge **22** is put into a chamber which is sealed. The chamber is connected to a vacuum level sensor and a vacuum pump, and a vacuum is applied (i.e., a vacuum is pulled at a validated rate). If a desired level of vacuum is not reached in a pre-validated time, the cartridge **22** is considered to have failed the leak test.

(92) Based on the results of the filter integrity test and the cartridge vacuum test, a determination that the solution of the filled product bag **26** is either sterile or has the potential of being compromised may be made with a high degree of certainty. Even if one filter **118**, **122** of the filter assembly **34** fails the filter integrity test, there is a high chance that the solution in the bag **26** is still sterile as both filters **118**, **122** of the filter assembly **34** would have to fail to compromise the solution. The filter integrity test performed in a filter integrity test machine and the vacuum test described above are not limited to those methods described herein, and may include different acceptable tests designed to assess the quality and performance of the filters **118**, **122** and cartridge.

(93) Turning now to FIG. **23**, a first exemplary method **500** of filling a plurality of product bags with sterile solution is generally described. The method **500** may be performed with or without the machine **400** and with the same, similar, or different cartridge **22**, **222** described herein.

(94) The method **500** begins with a step **504** of positioning the cartridge **22** onto a filling machine, such as the filling machine **400** of FIGS. **18**A-**18**D. While the following method is explained with reference to the first exemplary cartridge of FIGS. **2-3**, the second exemplary cartridge **222** of FIGS. **6**A-**6**C may be used as well in the method **500**. A first, unused and gamma-sterilized cartridge **22** is loaded onto a gantry system **416**, or other holding mechanism, of the machine **400**. During this step **504**, the peristaltic tubing **114** of the connection line **46** of the cartridge **22** is coupled the second pump **44**, and the reservoir **38** and filter assembly **34** are loaded to the machine **400** such that the reservoir **38** is at least partially disposed above the grid **56** and engaged with the load cell **412**. Next, the cartridge **22** is coupled to the feed line **18** in step **508**.

(95) A step **512** of activating the first pump **42** of the system **10** of FIG. **1** initiates the filling cycle to fill a plurality of bags **26** of the cartridge **22** with filtered solution. By activating the first pump **42**, the feed line **18** is purged of air and vented through the vent **164** while the isolation valve **165** is in the closed position. Subsequently, solution is pumped from the mix tank **14**, through the feed line **18**, the filter assembly **34**, and the connection line **46** of the cartridge **22**. This step also includes filling the reservoir **38** with a desired amount of sterile solution before filling the remainder of the cartridge **22** with solution. The reservoir **38** is coupled to the connection line **46**, disposed upstream from the plurality of bags **26**, and disposed downstream from the filter assembly

34. In step **516**, the solution from the reservoir **38** is used to at least partially fill one or more bladders **52** of the plurality of bags **26** of the cartridge **22** by activating the second pump **44**. The second pump **44** is disposed downstream from the reservoir **38** and upstream from the plurality of bags **26** coupled to the connection line **46**. The second pump **44** runs to first purge any air trapped in the connection line **46**, and then to fill each of the plurality of bags **26**, one at a time, with sterile solution.

(96) In step **520**, the method **500** includes sealing the stem **54** of each of the at least partially filled product bags **26** at a location between the connection line **46** and the bladder **52**, thereby creating one or more at least partially filled and sealed product bag **26**. Finally, each bag **26** is separated from the connection line **46** in step **524**. As previously described, the seal and cut assembly **404** of the machine **400** may automatically seal and cut each stem **54** of the product bags **26** after each bag **26** is filled with solution. In another example, however, the stems **54** of each bag **26** may be sealed and cut manually. Finally, after separating each of the at least partially filled and sealed product bags **26** from the connection line **46** in step **524**, the second pump **44** is reversed to recapture any unused solution from the cartridge **22**.

(97) The system **10**, machine **400**, and methods **500**, **600**, and cartridges **22**, **222**, **422**, **822** disclosed herein provide considerable advantages for producing sterile solution-filled containers. The machine **400** is modular, portable, and self-containing, allowing customization of a filling system to meet a particular facility's specifications or market demand. One exemplary machine **400** has a footprint of approximately 6′×7′. Additionally, the methods **500** and **600** described herein provide sterile solution bags **26** without using a sterilizing autoclave and/or expensive sterilization equipment required to sterilize the working environment and eliminate the risk of formulation degradation due to heat exposure. Because the system **10** and machine **400** do not need to be decontaminated or cleaned to the extent other systems require (i.e., down time), the system **10** and machine **400** are available 24 hours a day, seven days a week. Further, the self-contained and fully-automated machine **400** reduces the sterilization procedures necessary to be performed in terminal sterilization and aseptic filling processes, thereby resulting in fewer operator interventions. In one example, where a cartridge **22** includes 360 bags, an operator may only be required to load a cartridge every 15-30 minutes or for every 360 bags filled.

(98) The exemplary cartridges **22**, **222** of the disclosed system **10** also allow for greater production and may be customized according to a particular need. Each filling cycle includes processing multiple bags **26** in a single run. In one example, the cartridge **22** includes 90 bags **26** and the second exemplary cartridge **222** includes 180 bags **226**. In fact, the number of bags **26**, **226** per cartridge **22**, **222** may vary depending on the requirements of the system **10**. Further, multiple cartridges **22**, **222** may be connected together using aseptic connectors, such as the cartridge connector **50**, to increase the number of units processed before filter change is required.

(99) The configuration of the pre-gamma-sterilized cartridges **22**, **222** disclosed herein also reduces risk of contamination. The system **10** is entirely closed because the only connection between the solution source (i.e., the mix tank **14** and the feed line **18**) and the cartridge **22**, **222** is at the cartridge connector **50**. Once the solution passes through the filter assembly **34**, the sterile solution is never exposed to the environment before flowing into the product bags **26**, **226** thereby producing a product bag **26**, **226** filled with fluid that has been subject to terminal sterilization filtration. Moreover, the stem **54** is sealed and cut after filling such that no environmental exposure of the fluid can take place. In the case the sterilizing filters **118**, **122** are determined to be compromised, the bags **26**, **226** containing fluid from that filter would be contained and discarded without contaminating the processing equipment of the machine or other product bags being processed.

(100) In addition to the disclosed cartridge **22**, the filter assembly **34** also reduces risk of contamination and improves product safety. The filter assembly **34** has a high filtration capacity by including two filters **118**, **122** disposed in series. This dual-filter configuration provides a built-in

filter contingency in rare chance that one of the filters **118**, **122** fails during the filling cycle. The filter assembly **34**, which may be used to filter **360** individual bags **26** of solution (i.e., dual cartridge of 180 bags per grid **56**), reduces overall costs of the system **10** because more bags **26** are filled per filter **118**, **122**. Additionally, because there is a significantly decreased chance of both filters **118**, **122** failing, less bags **26** are discarded over time. Further, there are significantly fewer filter changes per batch resulting in fewer filter integrity tests. For example, instead of testing the filter for each bag (e.g., when there is a 1:1 ratio of filter to bag), one filter is tested for an entire batch of bags, which may be 360 bags.

(101) In another aspect of the cartridge **22**, the reservoir **38** serves various and important roles that increase efficiency and accuracy of the filling system **10**. In comparison to the filling time required in other terminal sterilization methods, the time for filling bags **26** of the system **10** disclosed herein is reduced significantly because solution is drawn directly from the reservoir **38** rather than from the filter assembly **34**. By drawing from the bag **38**, the filling cycle increases in efficiency and reduces strain typically placed on a filter assembly. This ensures that filling can be carried out at the maximum possible speed without increasing the pressure drop across the filter assembly **34** and thereby protecting the integrity of the filters **118**, **122**. The reservoir **38** also helps improve fill accuracy by removing the inherent variability introduced by the filter during its use cycle (i.e., as filter pores progressively clog up, the flow rate through the filter starts to change thereby negatively impacting fill accuracy).

(102) Accuracy is also increased because the reservoir **38** is disposed on the load cell **412**, which monitors the exact amount of solution disposed in the reservoir **38** at any time during the fill cycle. The system **10** does not have to account for a required amount of headspace in each given product bag **26** when filling each product bag **26** with solution because the trapped air in the connection line **46**, which is typically pushed into the product bag **26**, is initially purged and pushed into the reservoir **38** before the bags **26** are filled. This increases filling accuracy because only the amount of solution, rather than an additional estimated headspace created from the trapped air in the stem and/or connection line, needs to be measured and monitored.

(103) Additionally, the reservoir **38** improves the sustainability of the filling system **10** by recovering any unused sterilized solution of each filling cycle. Initially, the reservoir **38** serves as a volume that receives solution required to wet the filter assembly **34**, which would otherwise be discarded and/or wasted. Primarily, the reservoir **38** serves to minimize waste of the system **10** by receiving any unused solution (i.e., not delivered to a product bag **26**) from the distribution grid **56**. After all the solution is pulled back into the reservoir **38**, the contents of the reservoir **38** are returned to the mix tank **14** safely and without any contamination risk. This reduces solution waste and controls environmental contamination in a simple and safe way. Finally, the amount of solution used for filling the plurality of bags **26** is monitored closely for more precise delivery by mounting the reservoir **38** on the load cell **412**. Towards the end of the bag fill phase, the control system **402** of the machine **400** actively manages the amount of solution in the reservoir **38** to ensure that reservoir **38** is almost empty when the cycle ends.

(104) Preferred embodiments of this invention are described herein, including the best mode or modes known to the inventors for carrying out the invention. Although numerous examples are shown and described herein, those of skill in the art will readily understand that details of the various embodiments need not be mutually exclusive. Instead, those of skill in the art upon reading the teachings herein should be able to combine one or more features of one embodiment with one or more features of the remaining embodiments. Further, it also should be understood that the illustrated embodiments are exemplary only, and should not be taken as limiting the scope of the invention. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the aspects of the exemplary embodiment or embodiments of the invention, and do not pose a

limitation on the scope of the invention. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Claims

1. A cartridge assembly for a filling machine, the assembly comprising: a plurality of containers, each container including a volume and a stem connected to the volume; a connection line grid in fluid communication with each stem of the plurality of containers, the connection line grid including a first row connected to one or more containers of the plurality of containers and a second row connected to one or more containers of the plurality of containers; and a filter assembly coupled to the connection line grid; wherein the connection line grid includes a network of interconnected tubing defining a supply manifold, a return manifold, a first row, and a second row, the first row and the second row extending between the supply manifold and the return manifold.
2. The assembly of claim 1, wherein the filter assembly includes a first filter and a second filter arranged in series.
3. The assembly of claim 1, further comprising a reservoir coupled to the connection line grid and disposed upstream from the plurality of containers and downstream from the filter assembly, the reservoir including a volume, a first port, and a second port.
4. The assembly of claim 3, wherein the reservoir is disposed above, with respect to gravity, the connection line grid.
5. The assembly of claim 3, wherein the supply manifold of the connection line grid is coupled to the first port of the reservoir and the return manifold is coupled to the second port of the reservoir.
6. The assembly of claim 1, wherein the network of interconnected tubing includes at least one rigid portion connected to at least one flexible portion.
7. The assembly of claim 1, wherein each of the first and second rows includes a first end, a second end, and a fill manifold connecting the first and second ends, the first and second ends being flexible and the fill manifold being rigid.
8. The assembly of claim 7, wherein the supply manifold is coupled to the first end of each of the first and second rows and the return manifold is coupled to the second end of each of the first and second rows.
9. The assembly of claim 7, wherein the fill manifold of each of the first and second rows includes one or more ports corresponding to the one or more containers of each of the first and second rows, each port of the one or more ports in fluid communication with one stem of the one or more containers.
10. The assembly of claim 1, wherein each row of the first and second rows of the connection line grid is coupled to at least two of the plurality of containers.
11. The assembly of claim 1, wherein the plurality of containers includes a plurality of product bags, and wherein the volume is a bladder.
12. The assembly of claim 1, wherein the plurality of containers includes a plurality of vials.
13. The assembly of claim 1, wherein the plurality of containers includes a plurality of syringes.
14. The assembly of claim 1, further comprising sample bags coupled to each filter in the filter assembly, the sample bags configured to receive purged air and solution samples.
15. The assembly of claim 1, further comprising: a pump configured to move fluid through the connection line grid; and a reservoir coupled to the connection line grid, the reservoir disposed between the pump and the filter assembly.
16. The assembly of claim 15, wherein the reservoir is disposed above, with respect to gravity, the connection line grid.
17. The assembly of claim 15, wherein the return manifold of the connection line grid is coupled to an inlet port of the reservoir.

18. The assembly of claim 17, wherein the supply manifold of the connection line grid is coupled to an outlet port of the reservoir.