

**METHOD OF USING AN ULTRASONIC FLOW SENSOR TO MONITOR FILL WEIGHT ACCURACY OF CLINICAL,
COMMERCIAL, AND PROCESS DEVELOPMENT FILL/FINISH OPERATIONS**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Priority is claimed to U.S. Provisional Patent Application No. 63/455,847, filed March 30, 2023, the entire contents of which are hereby incorporated by reference herein.

FIELD OF THE DISCLOSURE

[0002] The present disclosure generally relates to monitoring a process of filling containers with liquid, and, more specifically to using one or more flow sensors to detect fill amount.

BACKGROUND

[0003] Drug product filling is a complex unit operation which is critical in ensuring high quality product is delivered to patients. Among other considerations, a good filling process must consistently deliver, within a tight tolerance, a consistent amount of drug product to every container so that all units can be judged both safe and efficacious according to scientifically determined action limits. Such consistency could, potentially, be ensured with 100% in-process control (IPC) of fill weight. One IPC approach is to weigh every dose on a scale of sufficient precision to confirm that the dose amount falls within the action limits. However, the mechanics of this process (in which an empty container is placed on a gravimetric weigh scale, tared, removed from the scale, filled, then returned to the scale and re-weighed) tend to be very time consuming. Therefore, there is a need for an alternative IPC that can ensure accurate and consistent dose amounts.

SUMMARY OF THE DISCLOSURE

[0004] In one example, a system for filling containers with liquid comprises a flow control device configured to transfer the liquid from a storage reservoir into a container via tubing and at least one sensor disposed at the tubing. The system further comprises one or more processors configured to cause the flow control device to transfer the liquid from the storage reservoir to the container via the tubing. The one or more processors of the system are further configured to receive from the at least one sensor a plurality of values indicative of a plurality of respective flow rates at the plurality of respective times within a fill-time interval and to compute, based at least in part in the plurality of the received values, an indication of fill amount. Still further, the one or more processors of the system are configured to compare the indication of fill amount to a target fill amount and to generate an indication of fill amount compliance.

[0005] In another example, a method for checking container fill amount compliance comprises causing, by one or more processors, a flow control device to transfer a liquid from a storage reservoir to a container via tubing. The method further comprises receiving, by the one or more processors and from at least one sensor disposed at the tubing, a plurality of values indicative of a plurality of respective flow rates at a plurality of respective times within a fill-time interval. Still further, the method comprises: i) computing, by the one or more processors, based at least in part on the plurality of the received values, an indication of fill amount; ii) comparing, by the one or more processors, the indication of fill amount to a target fill amount; and generating, by the one or more processors, an indication of fill amount compliance.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 schematically illustrates an example system for filling containers with liquid.

[0007] FIG. 2 schematically illustrates another example system for filling containers with liquid.

- [0008] FIG. 3 schematically illustrates an example system for detecting fill amount compliance.
- [0009] FIG. 4 schematically illustrates another example system for detecting fill amount compliance.
- [0010] FIG. 5 schematically illustrates an example contactless flow sensor disposed at a section of tubing.
- [0011] FIGS. 6A and 6B schematically illustrate a principle of operation of an ultrasonic flow sensor.
- [0012] FIGS. 7A and 7B schematically illustrate example flow profiles.
- [0013] FIG. 8 is a block diagram of an example method for checking container fill amount compliance.

DETAILED DESCRIPTION

[0014] The present disclosure relates to operating a system for filling dispensation containers (e.g., ampules, vials, cartridges, syringes, etc.) with liquids (e.g., therapeutic liquids such as chemical drugs, biopharmaceuticals, etc.) in clinical or commercial settings. The examples describe herein may supplement or replace gravimetric process control in filling operations with process control based, at least in part, on using flow sensors (e.g., ultrasonic, electromagnetic, etc.). Measuring dispensed amounts based on flow rates has a significant advantage in speed vis-à-vis gravimetric systems that measure each individual fill. Gravimetric process control systems that sample only a portion of filled containers can increase throughput. The improvement in throughput may come at the expense of potential product waste if a sample is out of compliance and a whole batch needs to be discarded. Thus, flow rate-based process control systems of the present disclosure can reduce product waste and improve efficiency in comparison to sampling gravimetric systems. Furthermore, flow rate-based process control systems of the present disclosure can be used to rapidly and effectively identify fill process problems, and thus offer a diagnostic advantage over gravimetric systems. The systems and methods of this disclosure are more broadly applicable to many container filling operations where fill precision and/or fill speed are of high importance. Additionally, systems and methods described in this disclosure can include flow rate measurement in filling operation during development work, ensuring robust process characterization and allowing operators to more easily detect and troubleshoot fill weight deviations.

[0015] The systems and methods described in the present disclosure overcome several challenges in converting flow rate measurements into indications of fill amounts. Some of these challenges are specific to filling processes involving doses of therapeutic liquids. For example, the absolute precision required to fill a volume of a fraction of a milliliter to several milliliters with high relative precision is considerably more challenging to achieve than equivalent relative precision for larger volumes. Rapid filling processes with small fill amounts may rely on frequent start and stop of pumping or valve operations. The rapid cycling of pumping or valve operation, in turn, leads to requirements in flow rate sampling as well as detection of start and stop times of each fill-time interval. Furthermore, sensitivity to possible contamination of therapeutic liquids requires minimal contact with equipment. Thus, pumps, valves, and sensors used in the systems described in the present disclosure may be contactless pumps, valves, and sensors. Peristaltic pumps, for example, used in filling operations may cause ripple in flow rates. Thus, the systems and methods of this disclosure may use suitable flow rate integration algorithms and/or other techniques for overcoming fill amount errors stemming from flow rate variations.

[0016] The described techniques may achieve results comparable or superior to techniques using gravimetric weigh scales, enabling 100%, non-invasive, non-destructive, non-product contact in-line assessment of fill weights with no negative impact to line speed or throughput.

[0017] FIG. 1 schematically illustrates an example system 110 for filling containers with liquid. The system 110 includes a flow control device 120, one or more sensors 130a, b, and a processing unit 140. Sensor 130b is represented with a dashed line to illustrate that sensor 130b is optional, and the example system 110 may be configured with only sensor 130a. The sensors 130a, b are in communicative connection with the processing unit 140 and in fluidic connection with the flow control device 120. The flow control device 120 may also be in fluidic connection with the processing unit 140. Furthermore, the flow control device 120 may be in fluidic connection with tubing 150 and, via the tubing 150, with a storage reservoir 160 and a container 170.

[0018] The flow control device 120 may include one or more pumps (e.g., peristaltic pump, a gear pump, a diaphragm pump, etc.), one or more valves, and/or any other suitable flow control elements. The flow control device 120 may be distributed throughout the fluidic portion of the system 110. For example, a pump may be disposed at the reservoir 160 or at one point along the tubing 150, while one or more valves may be disposed at different points along the tubing 150.

[0019] Sensors 130a, b may be ultrasonic, electromagnetic, or any other suitable flow sensors. Additionally or alternatively, at least one of the sensors 130a, b may be an imaging sensor, a particle velocimetry sensor, or any other suitable sensor type capable of measuring flow rate within the tubing 150. The system 110 may additionally include sensors for measuring fluid or environmental temperature, fluid or environmental pressure, fluid density, opacity, viscosity, and/or uniformity.

[0020] The processing unit 140 may include one or more processors. The one or more processors may be included in a single computing device or, in some examples may be distributed among multiple devices. For example, the processing unit 140 may have some components integrated into the sensors 130a, b, other components integrated into the flow control device 120, and still other components integrated into an overall process control and/or notification system. At least one of the one or more processors included in the processing unit 140 may be implemented in the cloud. At least one of the one or more processors included in the processing unit 140 may be included in a laptop or a mobile computing device. The one or more processors of the processing unit 140 may include one or more microcontrollers (μ Cs), single-core or multi-core central processing units (CPUs), graphical processing units (GPUs), field-programmable gate arrays (FPGAs) or any other suitable processor architecture.

[0021] The processing unit 140 may include memory elements communicatively connected to the one or more processors. The memory elements may include a read-only memory (ROM) component and a random-access memory (RAM) component, removable memory devices, etc. The memory elements may be communicatively connected to the one or more processors by way of bus structures including a memory bus or memory controller, a peripheral bus, or a local bus, etc., and may use any suitable bus architecture. By way of example, and not limitation, such architectures include the Industry Standard Architecture (ISA) bus, Micro Channel Architecture (MCA) bus, Enhanced ISA (EISA) bus, and Peripheral Component Interconnect (PCI) bus (also known as Mezzanine bus).

[0022] The processing unit 140 may be communicatively connected to the flow control device 120 and the sensors 130a, b by way of any combination of suitable wired and/or wireless connections.

[0023] The tubing 150 may be uniform or include multiple fluidically connected portions. The tubing 150 may be rigid, flexible, or include a combination of rigid portions and/or flexible portions. The tubing 150 may be composed of glass, metal, plastic (e.g., silicone, Teflon, etc.), or any other suitable material. The tubing 150 may include different portions with different inner and/or

outer diameters. The tubing may be terminated by a nozzle configured to direct the liquid into the container 170. The tubing 150 may have a diameter of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15 mm or any other suitable diameter.

[0024] The reservoir 160 may be a surge vessel, a vat, a tank, or any other suitable reservoir composed of glass, metal, plastic or any other suitable material or combination of materials. The reservoir 160 may include an outlet to connect to the tubing 150. The reservoir 160 may include one or more inlets through which the reservoir 160 may receive the liquid and/or gas to pressurize the reservoir 160. One or more sensors may be disposed within the reservoir 160 to monitor, for example, environmental conditions within the reservoir 160. One or more pumps and/or heating elements may be disposed at the reservoir 160 to control the environmental conditions within the reservoir 160. In some examples, the reservoir 160 may include an agitator or a mixing element to aid in mixing, homogenizing, or degassing of the liquid in the reservoir 160.

[0025] The liquid in the reservoir 160 may be a therapeutic, a drug, a biopharmaceutical, or any other liquid for filling the container 170. In some examples the liquid in the reservoir 160 is a suspension. The challenge of transferring the suspension from the reservoir 160 into the container 170 includes maintaining appropriate composition of the suspension.

[0026] The container 170 may be a syringe, an ampule, a cartridge, or any other suitable container for receiving the liquid from the reservoir 160. The container 170 may be made of glass, metal, plastic, or any other suitable material. The liquid may be an injectable therapeutic and the container 170 may be configured to contain one or more doses of the therapeutic.

[0027] In some embodiments, the system 110 may include multiple reservoirs with different liquids and multiple flow control devices configured to transfer liquids from the multiple reservoirs into the container 170 in appropriate relative ratios. A person skilled in the art can apply the techniques of this disclosure to implement measurements and/or controls for adding liquids from multiple reservoirs into the container with precise amounts of the different liquids from the correspondent reservoirs.

[0028] In operation, the flow control device 120 of the system 110 may transfer at least a portion of the liquid from the storage reservoir 160 to the container 170. A peak flow rate in the tubing 150 during transfer of liquid into the container 170 may be 0.1, 0.2, 0.5, 1, 2, 5, 10 mL/s or any other suitable peak flow rate. In some examples, the flow control device 120 may initiate and/or terminate the transfer based on a signal from the processing unit 140. That is, the processing unit 140 may cause the flow control device 120 to transfer, via the tubing 150, a portion of the liquid from the storage reservoir 160 to the container 170. In other examples, the flow control device 120 may operate independently of the processing unit 140. Furthermore, in some implementations, the flow control device 120 may be placed outside of a system for determining compliance of a container-filling process. In FIG. 1, to indicate that the flow control device 120 and the processing unit 140 need not communicate with each other, the arrow symbolizing a communicative connection between the processing unit 140 and the flow control device 120 is shown with a dashed line.

[0029] The sensors 130a, b disposed at the tubing 150 are configured to measure, directly or indirectly, as described in more detail below, flow rate of liquid flowing through the tubing 150. In some example, the flow rate is between 0.1 and 1 mL/s. The sensors 130a, b need not measure the flow rate directly. Instead, the sensors 130a, b may, for example, measure velocity of liquid flowing through the tubing 150. Even if velocity in the tubing 150 is not uniform, i.e., varies within the cross-section of the tubing 150, the sensors 130a, b may measure, effectively, an average velocity or, for that matter, any suitable indication of velocity. In some examples, the average velocity is between 1 and 100 cm/s. More generally, the sensors 130a, b may measure

any indication of flow rate. The processing unit 140 may convert any indication of flow rate into an accurate measure of flow rate using calibration data obtained as described in more detail below with reference to FIGS. 2, 7, and 8. It should be noted, that sensor output may have a different relationship to flow depending, for example, on flow properties, such as laminarity of the flow and or properties of the liquid.

[0030] In some examples, the sensors 130a, b may transduce a physical property of flow, such as velocity, into an analog voltage or current. In other examples, the sensors 130a, b may be integrated with analog-to-digital (A/D) converters and configured to generate a digital signal indicative of flow rate. Such sensors may transfer the digital data indicative of flow rate measurements to the processing unit 140 using any suitable wired or wireless interface. The sensors 130a, b may have multiple outputs, generating a plurality of signals, whether analog or digital. Besides signals indicative of flow rate, the sensors 130a, b may generate signals indicative of internal amplitude of transduction and or diagnostic signals, as described in more detail with reference to FIGS. 6A, B.

[0031] The sensors 130a, b may be configured to sample values indicative of flow rate at regular time intervals indicated by sampling frequency or sampling. In other examples, the sensors 130a, b may be configured to generate signals indicative of flow rates based on received trigger signals. For example the processing unit 140 may generate trigger signals to request samples from the sensors 130a, b.

[0032] The processing unit 140 may read or receive, whether in real time or with some delay, some or all the values encoded in the signals generated by the sensors 130a, b. As described above, the values may be analog values or digital values. The processing unit may digitize analog values received from the sensors 130a, b using an A/D converter. Along with the values indicative of flow rates received from the sensors 130a, b, the processing unit 140 may receive or generate values indicative of times associated with the flow rates values. At least some of the values indicative of times associated with the flow rates values may correspond to a fill-time interval, i.e., the time interval during which the liquid flowing through the tubing 150 is transferred into the container 170.

[0033] In some examples, the fill-time interval may correspond to a time interval or a sequence of time intervals during which the flow control device 120 is continually transferring the liquid into the container 170. That is, the flow control device 120 may cause the flow of liquid to be intermittent, with one or more filled-time intervals interrupted with substantially zero flow. Additionally or alternatively, the fill-time interval may correspond to a time interval during which there is a fluidic connection between the tubing 150 and the container 170. For example, during a period of substantially uninterrupted flow of liquid through the tubing 150, a robotic system (or any other suitable method) may switch the container 174 another such container. The processing unit 140 may receive or generate values indicative of time intervals during which a fluidic connection exists between the tubing 150 and the container 170 and during which the flow control device 120 is transferring liquid to the container 170. In some examples, the processing unit 140 may generate trigger signals causing changes in the flow of the liquid through the tubing 150 and/or trigger signals causing the replacement of the container 170 with another such container. In other examples, the processing unit 140 may receive indications of time when the flow of liquid started and/or stopped, and/or when the container 170 was in fluidic connection with the tubing 150.

[0034] The processing unit 140 may compute, based at least in part on the plurality of the received values indicative of flow rates, and indication of fill amount corresponding to the amount of liquid transferred into the container 170 during the fill-time

interval or, equivalently, a sequence of fill-time intervals comprising a total fill-time interval or fill time. The computation may likewise be based on the indications of times corresponding to the fill-time interval received and/or generated by the processing unit 140. To compute the indication of fill amount, which for simplicity can be referred to as the fill amount, the processing unit 140 may numerically integrate flow rate of the liquid into the container 170 during the total fill time. For simplicity, the total fill time may be referred to as the fill-time interval, with the understanding that the fill-time interval may comprise a sequence of fill-time intervals. That is, the discussion below will assume that the total duration during which the container 170 receives the liquid is represented by a single fill-time interval. The total fill time for the container 170 may be between 0.1, 0.2, 0.5, 2, 5, 10 s or another suitable time.

[0035] Upon computing the fill amount, the processing unit 140 may compare the fill amount to a target fill amount. In some examples, the fill amount and the target fill amount are between 0.2 mL and 40 mL and/or between 0.2 mg and 40 mg. The comparison may include computing the absolute value of difference between the fill amount and the target fill amount as well as whether the fill amount is greater than the target fill amount or less than the target fill amount. In some examples, the processing unit 140 may perform a comparison of analog signals. To that end, the processing unit 140 may use one or more comparators to generate one or more respective binary outputs by comparing an integrated analog output of a sensor (e.g., sensor 130a or b) with a reference voltage. Additionally or alternatively, the processing unit 140 may include an A/D converter following a differential amplifier to digitize a difference between integrated sensor voltage output and a reference voltage. Still another examples the processing unit 140 may perform the comparison in digital domain. To that end, the processing unit 140 may receive or generate a binary value with a suitable resolution (e.g., 8-bit, 12-bit, 16-bit, 24-bit, etc.) indicative of fill amount and compare the binary value to the target fill amount value stored in memory of the processing unit 140.

[0036] Based on comparing the fill amount computed based on sensor measurements with the target fill amount, may generate an indication of fill amount compliance. For example, the measured fill amount may be indicated as compliant when it falls within a range of the target fill amount. The processing unit 140 may receive the target amount and compliance range to generate compliance indications. The processing unit 140 may store a log of computed fill amounts and/or generated compliance indications. Furthermore, the processing unit 140 may display the indication of compliance on a display unit, as described in more detail below with reference to FIG. 2.

[0037] FIG. 2 schematically illustrates another example system 210 for filling containers with liquid. The example system 210 includes a flow control device 220 (which may be the flow control device 120), one or more sensors 230a, b (which may be sensors 130a, b), and a processing unit 240 (which may be the processing unit 140). The system may further include tubing 250 (which may be tubing 150) and a reservoir 260 (which may be the reservoir 160) which serves as the source of liquid to be transferred into the container 270 (which may be the container 170).

[0038] The system 210 further includes a display unit 280 communicatively connected to the processing unit 240. The display unit 280 may include a liquid crystal display (LCD) an organic light-emitting diode display (OLED), or any other suitable matrix display. Additionally or alternatively, the display unit 280 may include one or more light indicators such as bulbs and/or light emitting diodes (LEDs). Furthermore, the display unit 280 may include one or more sound generators (e.g., buzzers, speakers, etc.) configured to generate sound alerts (for example, to indicate compliance). In some examples, a display belonging to the display unit 280 may be integrated into a user device (e.g., laptop, tablet, smart phone, etc.). In any case, a

graphical user interface may be rendered on a display of the display unit 280, and the processing unit 240 may display the indication of fill amount compliance via the graphical user interface with, for example, a virtual button or a bar graph configured to change color as the bar passes a threshold, and/or a text alert. Furthermore, the display unit 280 may generate a sound alert as a pattern of buzzes, a pattern of beeps, and/or a prerecorded or synthesized speech message.

[0039] The processing unit 240 of the system 210 may be in communicative connection with a gravimetric scale 290 or, simply, scale 290. In some examples, the scale 290 may be included in the system 210. Using the scale 290, the processing unit 240 may perform one or more calibrations as described in more detail below, with reference to FIGS. 7A and 7B. In general terms, the processing unit 240 may record one or more weights associated with respective fill amounts computed based on measurements from sensors 230a, b and create a lookup table and/or a formula relating fill amounts to gravimetric leave measured weights. In other examples, the system 210 may include a device (e.g., a camera, a level sensor, etc.) for measuring liquid volume or liquid level within the container 270. The processing unit 240 may use the measured liquid volume or liquid level for calibrating fill amounts computed by the processing unit 240 based on measurements of the sensors 230a, b.

[0040] In some examples, the processing unit 240 may control the flow control device 220 to perform a variety of calibrations, such as the ones outlined above. For example, the processing unit 240 may cause the flow control device 220 to cause the flow of liquid in the tubing for one or more time periods of any suitable durations. The processing unit may use, for each of the time periods, respective weights or weight increments measured by the scale 292 to calibrate flowrates measured by sensors 230a, b. Additionally or alternatively, the processing unit 240 may cause the flow control device to interrupt the flow of liquid in the tubing 250 and receive baseline measurements from the sensors 230a, b.

[0041] FIG. 3 schematically illustrates an example system 315 for detecting fill amount compliance which may be a portion of a system for filling containers with liquid (e.g., system 110 or 210). The system 315 includes a processing unit 340 (which may be the processing unit 140 or 240) and two flow sensors 330a, b (which may be the sensors 130a, b or the sensors 230a, b). Note that the system 315 need not include a flow control device. Generally, a flow control device need not be included in a system for detecting fill amount compliance, but a flow control device (e.g., the flow control device 120 or 220) may be included in a larger system for filling a container with liquid which may include the system 315.

[0042] The sensors 330a, b of the system 315 may be disposed, respectively, at two tubing sections 350a, b which may be sections of tubing 150 or 250. The tubing sections 350a, b fluidically communicate each other and are connected in series to transfer liquid into a container 370 (which may be the container 170 or 270). The tubing section 350a may have a thinner inner diameter than the tubing section 350b. Consequently, for liquid transfer with a constant flow rate flow velocity in section 350a may be faster than flow velocity in section 350b. In some examples the tubing sections 350a, b may be connected via an adapter or an adapter section with a gradually changing inner diameter, for example, to avoid the possibility of creating turbulence.

[0043] The inner diameter of section 350b may be larger than the inner diameter of section 350a by 10%, 20%, 40%, 50%, 100% or any other suitable ratio. For example, the inner diameter of section 350b may be 2 mm, while the diameter of section 350b may be 3 mm, i.e., 50% larger than the diameter of section 350a.

[0044] The system 315 may use the two sensors 330a, b disposed at the two tubing sections 350a, b in a variety of ways. First, as with two sensors (e.g., sensors 130a, b or 230a, b) disposed at same-diameter sections of tubing (e.g., tubing 150 or

250), the processing unit 340 may receive values from the two sensors 350a, b and average them to reduce noise. Additionally or alternatively, the processing unit 340 may correlate time sequences of flow rate values from the two sensors 350a, b to identify changes in intermittent flow, e.g., forward or back boundaries of a liquid section, as discussed with reference to FIG. 5. Furthermore, also as discussed with reference to FIG. 5, the processing unit 340 may identify flow anomalies (e.g., unexpected discontinuities or bubbles) by correlating time sequences of flow values. Using sensors 330a, b, disposed at different diameter tubing sections 350a, b, the system 315 may enable additional insight into properties of flow or sensor performance. Because the flow of liquid is substantially incompressible, average velocities of flow in differently sized tubing sections 350a, b are inversely proportional to the areas of respective tubing cross-sections. For example, if the cross-section diameter of tubing section 350b is 20% larger than the cross-section diameter of tubing section 350a, the average flow velocity in the section 350a should be 44% faster than in the section 350b (because area varies as the square of diameter). Although the values indicative of flowrates received from the sensors 330a, b may not have the same ratio as the respective average velocities of flow (due to the particularities of flow velocity measurements) the relationship between the two values can be deduced from calibration. Deviations from the relationship deduced from calibration may indicate changes or anomalies in the flow. Furthermore, the system 315 may use velocity measurements at differently sized tubing sections 350a, b to improve accuracy of flow velocity measurements at least because either the faster or the slower velocity may be closer to optimal range of a flow rate sensor 330a or b.

[0045] FIG. 4 schematically illustrates another example system 415 for detecting fill amount compliance. The system 415 includes a processing unit 440 (which may be the processing unit 140, 240 or 340) and three flow sensors 430a-c. The sensors 430a-c are disposed at tubing 450 configured to transfer liquid into a container 470 (which may be the container 170, 270, or 370). The sensors 430a-c need not be disposed with equal spacing. The system 415 may use the three sensors 430a-c in a variety of ways. First, average and values from multiple sensors may increase measurement accuracy. Second, the processing unit 440 may correlate time sequences of values of the three sensors 430a-c to identify changes in intermittent flow, e.g., forward or back boundaries of a liquid section, as discussed with reference to FIG. 5. Furthermore, also as discussed with reference to FIG. 5, the processing unit 440 may identify flow anomalies (e.g., unexpected discontinuities or bubbles) by correlating time sequences of flow values. Furthermore, the system 415 may use the three sensors for diagnostic purposes. For example, when values generated by one of the sensors are inconsistent with the values generated by the other two, the outlier value may be ignored and the correspondence sensor may be flagged as malfunctioning.

[0046] FIG. 5 schematically illustrates an example contactless flow sensor 530 (which may be one of the flow sensors 130a, b, 230, a, b, 330 a, b or 430a-c) disposed at a section of tubing. Having a contactless sensor may be particularly important in medical applications. The sensor 530 may be an ultrasonic sensor, an electromagnetic sensor, an optical sensor, or another suitable contactless sensor. The sensor may include a channel 532 configured to match the diameter of the tubing. In some examples, a sleeve may be placed over the tubing to provide a better contact with the flow sensor 530. As discussed above, the sensor 530 may aid in identifying discontinuities within intermittent flow. For example, a system (e.g., system 110, 210, 315 or 415) may use the sensor 530 to identify a forward boundary 555a or a back boundary 555b separating a liquid portion 555c from an empty (i.e., gas-filled) portion of the intermittent flow. Furthermore, the system may use the sensor 530 to identify an air pocket or bubble 555e or another anomaly within the liquid portion 555c. The system may further include vibration isolation, thermal isolation, and electrical shielding to reduce measurement noise.

[0047] FIGS. 6A, B schematically illustrate a principle of operation of an ultrasonic flow sensor 630 (which may be one of the flow sensors 130a, b, 230, a, b, 330 a, b, 430a-c or 530). The sensor may include a channel 632 and four ultrasound transducers 635a-d. The channel 632 is configured to tightly clamp around a section of tubing, creating a sonically conductive path, particularly when the tubing is filled with liquid. Of the transducers 635a-d, two 635a, b may be used as ultrasound transmitters and two 635c-d may be used as ultrasound receivers. Three arrows within the channel 632 schematically illustrate a flow velocity profile within the channel 632. Closer to the center, a liquid may move faster than the liquid near the edge (e.g., during laminar flow). In some examples, the flow may be turbulent (e.g., at higher flow rates) or transitional between laminar and turbulent flow. Curved dashed lines between the transducer 635a and the transducer 635d in FIG. 6A and, in FIG. 6B, between the transducer 635b and the transducer 635c schematically illustrate sonic wave fronts. Leaving ultrasonic transmitters 635a, b, the wave fronts are equally spaced in FIGS. 6A and 6B. However, in FIG. 6A, the wave fronts arrive at the ultrasonic receiver 635d with wider spacing than the wave fronts arriving at the ultrasonic receiver 635c in FIG. 6B, because ultrasonic waves move with the flow in FIG. 6A and against the flow in FIG. 6B. The change in wave fronts spacing can be thought of as an example of the Doppler effect, and the received ultrasound frequency in FIG. 6A is lower than the ultrasound frequency in FIG. 6B. The sensor 630 may include electronic components to generate an analog or a digital output indicative of flow velocity based on the difference in the received ultrasound frequencies. In some examples, rather than transmitting continuous ultrasound waves, the sensor 630 may transmit ultrasound pulses. When using ultrasound pulses, the sensor 630 may generate an output indicative of flow velocity based on the difference of times of transit (time transit difference or TTD) of ultrasonic pulses with the flow and against the flow. Additionally or alternatively, the sensor 630 may be configured to use phase differences in received ultrasound signals with the flow and against the flow. The phase-difference method may be particularly advantageous when time differences and frequency differences of the TTD and Doppler methods are small. Furthermore, the sensor 630 may output values for received signal strengths. A system (e.g., system 110, 210, 315 or 415) may use output values indicative of signal strengths to identify boundaries of liquid in intermittent flow, sound transduction problems, and/or changes in one or more properties of liquid flowing within the tube disposed in the channel 632. Furthermore, the system may use the various outputs above to generate failure mode alerts indicative of fill quality failure modes (e.g., dripping, splashing, bubble formation, etc.) and/or alerts indicative of system malfunctions (e.g., blockage, etc.) as described in more detail with reference to FIG. 8. During a testing or calibration process, the system may be configured to generate a set of failures of different types during which sensor outputs (e.g., flow rates, signal strengths, etc.) may be sampled. Based on the generated set of failures and corresponding data, a classifier for identifying failure rates may be generated. During operation, the system may then use classifiers to estimate probabilities of different types of failure and generate alerts when respective probabilities exceed respective threshold.

[0048] FIGS. 7A and B illustrate example flow profiles during operation of a system (e.g., system 110 or 210). The graphs in FIGS. 7A and B illustrate samples of flow rate as a function of time. The system may cause a flow control device to keep flow rate constant during an interval of 100 ms or longer (as in FIG. 7A), for example to generate a fill of 10 mL or larger to use in flow rate calibration, as discussed in more detail below with reference to FIG. 8. The flow rate during a normal container fill operation, on the other hand, may include short bursts of flow rate, to generate with each burst a smaller fill volume (e.g., < 2 mL). It should be noted that during calibration, a larger calibration volume (e.g., > 10 mL) may be filled in multiple bursts instead of using a constant flow rate during a single time interval, as in FIG. 7A. Though not visible in FIGS. 7A and B, flow rate profiles may

include starting and stopping ramps. The starting and starting ramps may be substantially linear, each with a substantially constant slope, or may have any other suitable shape.

[0049] FIG. 8 illustrates an example method 800 of for checking container fill amount compliance. The method 800 may be executed, at least in part, by one or more processors of the processing units 140, 240, 340, or 440 of the systems 110, 210, 315 or 415 discussed above with reference to FIGS. 1-4. In some examples, the method 800 may be executed, at least in part, by processors external to the systems 110, 210, 315 or 415.

[0050] At block 810, the method 800 includes causing, by one or more processors, a flow control device (e.g., flow control device 120 or 220) to transfer a liquid from a storage reservoir (e.g., storage reservoir 160 or 260) to a container (e.g., container 170, 270, 370 or 470) via tubing (e.g., tubing 150, 250, 450 or tubing segments 350a, b). The tubing may be terminated by a nozzle configured to direct flow into the container.

[0051] At block 820, the method 800 includes receiving, by the one or more processors and from at least one sensor disposed at the tubing, a plurality of values indicative of a plurality of respective flow rates at a plurality of respective times within a fill-time interval. The plurality of times for which the flow rate values are received may include regularly spaced times based on a sampling rate (equivalently, sampling frequency or sampling period). The sampling rate may be between 10 Hz and 1 kHz (10 to 1000 samples/s), for example. The fill-time interval may be between 0.1 and 10 seconds. It may be advantageous to have more sample points during a fill time interval. There is, however, a trade-off between sampling rate and noise per sample. Thus, for continuous flow, having a higher sampling rate may not necessarily decrease noise in the estimate of average flow rate. On the other hand, a higher sampling rate may help identify start and stop points of the flow, particularly when a ramp-up and ramp-down profiles of flow are not well-known. Furthermore, besides random variations due to thermal noise, systemic noise may affect the samples. In particular, a peristaltic pump may cause flow pulsations. Coupling of alternating current (AC) power frequencies (e.g., 50 Hz, 60 Hz, etc.) onto a sensor signal may likewise cause systemic periodic fluctuations. To alleviate systemic noise issues, the method 800 may include receiving, by the one or more processors, one or more indications of at least one of i) an indication of measurement noise, ii) an indication of periodic flow rate perturbations, and/or iii) an indication of line voltage variations. The method 800 may further include changing the sampling rate based on the received one or more indications. One approach may include increasing the sampling rate beyond the Nyquist rate of signal fluctuations. Another approach may include adjusting the sampling rate to avoid aliasing effects. For example, the method 800 may include adjusting the sampling rate to match or be a fraction of a flow fluctuation frequency caused by the peristaltic pump. Furthermore, to avoid the effect of inconsistently sampling with respect to phase of fluctuations caused by the peristaltic pump, the method may include adjusting the sampling phase. The method 800 may further include generating, by the one or more processors, a trigger signal for synchronizing operation of the flow control device and the sampling rate.

[0052] At block 830, the method 800 includes computing, by the one or more processors, based at least in part on the plurality of the received values, an indication of fill amount. The indication of fill amount may be referred to as the fill amount to which the indication may be converted using appropriate calibration and/or other multipliers. Generally, computing the fill amount includes numerical integration of flow rate samples by summing up sample values or using any other suitable numerical integration method.

[0053] Computing the fill amount using numerical integration may include determining, by the one or more processors, a start time and an end time of the fill time interval based at least in part on the received plurality of values indicative of the plurality of respective flow rates at the plurality of respective times within the fill-time interval. For example, the method 800 may include determining a start time and/or a stop time by comparing measured flow rate to a threshold. In other examples, the method 800 may include determining a slope correspondent to a ramp-up of flow rate or a ramp down of flow rate and finding a zero intercept to identify a start time and/or a stop time.

[0054] Computing the fill amount may include computing a fill weight. To that end, the method 800 may include obtaining, by the one or more processors, an estimate of density of the liquid. Computing the fill weight may then be based on the estimate of density. Obtaining the estimate of density may include receiving information about the liquid (e.g., the fluid composition), measuring environmental parameters such as temperature, pressure, and/or humidity. Additionally or alternatively, obtaining the estimate of density may include performing a calibration. The calibration may include weighing (e.g., using the scale 290) any suitable filled container and subtracting the tare weight of the container. Calibration is described in more detail below with reference to block 860.

[0055] At block 840, the method 800 includes comparing, by the one or more processors, the indication of fill amount to a target fill amount. The method 800 may perform the comparison in analog or in digital domain as described in more detail above with reference to FIG. 1.

[0056] At block 850, the method 800 includes generating, by the one or more processors, an indication of fill amount compliance. To that end, the method 800 may include comparing the difference between the measured fill amount and the target fill amount to a threshold indicative of assigned tolerance. The tolerances for a positive excursion with respect to the target amount and the negative excursion with respect to the target amount need not be the same. The tolerances may be set for a particular fill process run and may depend on the liquid, the target fill amount, and/or the type of container to be filled.

[0057] The method 800 may further include generating an alert based on the indication of fill amount compliance. The alert may be a visual alert or a sound alert generated at a display unit (e.g., display unit 280). Additionally or alternatively, the method 800 may include generating one or more alerts indicative of one or more failure modes and/or other malfunctions. Alerts may include: indication of sensor malfunction (e.g., as described with reference to FIG. 4), indication of an air pocket in the liquid (e.g., as described with reference to FIG. 5), indication of dripping, indication of blockage (e.g., in a nozzle), and/or other suitable indications. The indication of dripping may be generated based on measuring or detecting a non-zero flow rate when the flow rate should nominally be zero. The indication of blockage may be generated based on measuring or detecting a flow rate value of line with the expected flow rate value. More generally, sensor data may be correlated to independently-detected problems or failures to extract data features indicative of the respective problems and failures. The system may use digital signal processing methods (e.g., correlation filters) and/or machine learning models to detect failures modes and/or other problems. The system may compare an output of a suitable digital filter and/or a suitable machine learning model to a threshold for a particular alert and issue the alert if the threshold is exceeded. The method 800 may include generating an interface to allow a user to select thresholds for different alerts.

[0058] At an optional block 860, the method 800 may include receiving, by the one or more processors and from the at least one sensor, a calibration flow value and computing the indication of fill amount based at least in part on the received calibration

flow value. In one example, the calibration flow value may be a baseline or a zero flow value generated by a sensor. To obtain the baseline value, the method 800 may include causing, by the one or more processors, the flow control device to prevent transfer of the liquid during a baseline calibration time interval. Computing the indication of fill amount may be based at least in part on the received baseline value.

[0059] Additionally or alternatively, calibration may include determining one or more conversion multipliers for converting a numerical integration of flow rate indicators to a fill amount. To obtain the conversion factors, the method 800 may include causing, by the one or more processors, the flow control device to transfer the liquid with a constant flow rate during a flow rate calibration time interval, as discussed with reference to FIGS. 7A, B. The method 800 may further include receiving, by the one or more processors and from the at least one sensor, a calibration flow value or a set of calibration flow values during the flow rate calibration time interval. The method 800 may further include numerically integrating the flow rate values during the flow rate calibration time interval. Still further, the method 800 may include an independent measurement of an amount of liquid accumulated in a container during the flow rate calibration time interval. The independent measurement may be a volume measurement and/or a weigh measurement, e.g., using the scale 290 in FIG. 2. As discussed with reference to FIGS. 7A, B., the calibration amount need not be the same as the target amount. In some examples, the calibration amount may be larger than the target amount by a factor of 2, 5, 10, 20, 50, 100 or any other suitable factor. The calibrations may be performed for different liquids, different flow rates, different environmental conditions, etc. and may compensate for varying liquid density and accuracy of sensor measurements.

[0060] The calibration process described above may include a series of calculations. For example, the calibration process may include accumulating liquid in a container during a calibration time interval (e.g., as illustrated in FIG. 7A). The system may compute an estimate of mass flow rate and volume flow rate corresponding to a sensor output during calibration as:

$$\mu_{cal} = \frac{m_{cal}}{t_{cal}} \quad Q_{cal} = \frac{\mu_{cal}}{\rho}$$

where μ_{cal} is flow rate during calibration, m_{cal} is mass accumulated in a container during calibration (e.g., measured by the scale 290), Q_{cal} is volume flow rate, and ρ is the density of the liquid. In some examples, ρ may be an external input into the calculation based on the predetermined density of the liquid. In other examples, ρ may be computed based on measuring the volume of liquid accumulated in the container during calibration (e.g., by measuring the liquid level within the container of known cross section). The system may compute the mass and volume flow rates during filling operations as

$$\mu_{meas} = \frac{\mu_{cal}}{V_{cal}} V_{meas} \quad Q_{meas} = \frac{Q_{cal}}{V_{cal}} V_{meas}$$

where μ_{meas} and Q_{meas} are, respectively, mass and volume flow rates during a single fill and V_{meas} and V_{cal} are integrated voltages (or other integrated output values as described above), respectively, during measurement and during calibration.

[0061] The method 800 may include performing calibrations at different flow velocities, for different inner tube diameters, under different environmental conditions, etc. In some examples, the calibration may include generating a calibration profile equivalent to multiple fill operation profiles (e.g., as in FIG. 7B vs FIG. 7A). Furthermore, during the calibration process, the method 800 may include statistically analyzing the sequence of samples (e.g., as illustrated in FIGS. 7A and B) to generate an estimate of sensor noise. In some examples, the system may vary sampling rate to find optimal sampling rate to reduce total

noise during integration. Additionally or alternatively, the method 800 may include generating an alert in the noise during calibration exceeds a threshold.

[0062] Additional considerations pertaining to this disclosure will now be addressed.

[0063] Some of the figures described herein illustrate example block diagrams having one or more functional components. It will be understood that such block diagrams are for illustrative purposes and the devices described and shown may have additional, fewer, or alternate components than those illustrated. Additionally, in various embodiments, the components (as well as the functionality provided by the respective components) may be associated with or otherwise integrated as part of any suitable components.

[0064] Embodiments of the disclosure relate to a non-transitory computer-readable storage medium having computer code thereon for performing various computer-implemented operations. The term “computer-readable storage medium” is used herein to include any medium that is capable of storing or encoding a sequence of instructions or computer codes for performing the operations, methodologies, and techniques described herein. The media and computer code may be those specially designed and constructed for the purposes of the embodiments of the disclosure, or they may be of the kind well known and available to those having skill in the computer software arts. Examples of computer-readable storage media include, but are not limited to: magnetic media such as hard disks, floppy disks, and magnetic tape; optical media such as CD-ROMs and holographic devices; magneto-optical media such as optical disks; and hardware devices that are specially configured to store and execute program code, such as ASICs, programmable logic devices (“PLDs”), and ROM and RAM devices.

[0065] Examples of computer code include machine code, such as produced by a compiler, and files containing higher-level code that are executed by a computer using an interpreter or a compiler. For example, an embodiment of the disclosure may be implemented using Java, C++, or other object-oriented programming language and development tools. Additional examples of computer code include encrypted code and compressed code. Moreover, an embodiment of the disclosure may be downloaded as a computer program product, which may be transferred from a remote computer (e.g., a server computer) to a requesting computer (e.g., a client computer or a different server computer) via a transmission channel. Another embodiment of the disclosure may be implemented in hardwired circuitry in place of, or in combination with, machine-executable software instructions.

[0066] As used herein, the singular terms “a,” “an,” and “the” may include plural referents, unless the context clearly dictates otherwise.

[0067] As used herein, the terms “approximately,” “substantially,” “substantial” and “about” are used to describe and account for small variations. When used in conjunction with an event or circumstance, the terms can refer to instances in which the event or circumstance occurs precisely as well as instances in which the event or circumstance occurs to a close approximation. For example, when used in conjunction with a numerical value, the terms can refer to a range of variation less than or equal to $\pm 10\%$ of that numerical value, such as less than or equal to $\pm 5\%$, less than or equal to $\pm 4\%$, less than or equal to $\pm 3\%$, less than or equal to $\pm 2\%$, less than or equal to $\pm 1\%$, less than or equal to $\pm 0.5\%$, less than or equal to $\pm 0.1\%$, or less than or equal to $\pm 0.05\%$. For example, two numerical values can be deemed to be “substantially” the same if a difference between the values is less than or equal to $\pm 10\%$ of an average of the values, such as less than or equal to $\pm 5\%$, less than or equal to $\pm 4\%$, less than

or equal to $\pm 3\%$, less than or equal to $\pm 2\%$, less than or equal to $\pm 1\%$, less than or equal to $\pm 0.5\%$, less than or equal to $\pm 0.1\%$, or less than or equal to $\pm 0.05\%$.

[0068] Additionally, amounts, ratios, and other numerical values are sometimes presented herein in a range format. It is to be understood that such range format is used for convenience and brevity and should be understood flexibly to include numerical values explicitly specified as limits of a range, but also to include all individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly specified.

[0069] While the present disclosure has been described and illustrated with reference to specific embodiments thereof, these descriptions and illustrations do not limit the present disclosure. It should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the present disclosure as defined by the appended claims. The illustrations are not necessarily drawn to scale. There may be distinctions between the artistic renditions in the present disclosure and the actual apparatus due to manufacturing processes, tolerances and/or other reasons. There may be other embodiments of the present disclosure which are not specifically illustrated. The specification (other than the claims) and drawings are to be regarded as illustrative rather than restrictive. Modifications may be made to adapt a particular situation, material, composition of matter, technique, or process to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the claims appended hereto. While the techniques disclosed herein have been described with reference to particular operations performed in a particular order, it will be understood that these operations may be combined, sub-divided, or reordered to form an equivalent technique without departing from the teachings of the present disclosure. Accordingly, unless specifically indicated herein, the order and grouping of the operations are not limitations of the present disclosure.

CLAIMS

1. A system for filling containers with liquid, the system comprising:
a flow control device configured to transfer a liquid from a storage reservoir into a container via tubing;
at least one sensor disposed at the tubing; and
one or more processors configured to:
cause the flow control device to transfer at least a portion of the liquid from the storage reservoir to the container via the tubing;
receive from the at least one sensor a plurality of values indicative of a plurality of respective flow rates at a plurality of respective times within a fill-time interval;
compute, based at least in part on the plurality of the received values, an indication of fill amount;
compare the indication of fill amount to a target fill amount; and
generate an indication of fill amount compliance.
2. The system of claim 1, further comprising:
a scale, configured to measure weight of one or more filled containers.
3. The system of claims 1 or 2, wherein the one or more processors are further configured to generate a trigger signal for the flow control device.
4. The system of any one of claims 1-3, wherein the target fill amount is between 0.2 mL and 40 mL or between 0.2 mg and 40 mg.
5. The system of any one of claims 1-4, wherein the at least one sensor includes an ultrasonic sensor.
6. The system of any one of claims 1-5, wherein the at least one sensor includes a first sensor and a second sensor configured to measure a first flow rate and a second flow rate at a first section of tubing and a second section of tubing, respectively.
7. The system of claim 6, wherein an inner diameter of the first section of tubing is at least 10% bigger than an inner diameter of the second section of tubing.
8. The system of any one of claims 1-7, wherein the at least one sensor includes at least three sensors.
9. The system of any one of claims 1-8, further comprising:
a display device configured to generate a visual and/or an auditory representation of the indication of fill amount compliance.
10. The system of any one of claims 1-9, wherein the flow control device includes a peristaltic pump.

11. A method for checking container fill amount compliance, the method comprising:
 - causing, by one or more processors, a flow control device to transfer a liquid from a storage reservoir to a container via tubing;
 - receiving, by the one or more processors and from at least one sensor disposed at the tubing, a plurality of values indicative of a plurality of respective flow rates at a plurality of respective times within a fill-time interval;
 - computing, by the one or more processors, based at least in part on the plurality of the received values, an indication of fill amount;
 - comparing, by the one or more processors, the indication of fill amount to a target fill amount; and
 - generating, by the one or more processors, an indication of fill amount compliance.
12. The method of claim 11, further comprising:
 - obtaining, by the one or more processors, an estimate of density of the liquid;
 - wherein:
 - computing the indication of fill amount includes computing an indication of fill weight based at least in part on the estimate of density of the liquid; and
 - the target fill amount is a target fill weight.
13. The method of claim 12, wherein obtaining the estimate of density includes measuring weight of one or more filled containers.
14. The method of claim 12 or 13, wherein obtaining the estimate of density includes an estimate of composition of the liquid.
15. The method of any one of claims 11-14, wherein at least some of the plurality of respective times within the fill-time interval are arranged at regular intervals determined by a sampling rate, and wherein the method further comprises controlling the sampling rate.
16. The method of claim 15, further comprising:
 - receiving, by the one or more processors, one or more indications of at least one of i) an indication of measurement noise, ii) an indication of periodic flow rate perturbations, and/or iii) an indication of line voltage variations; and
 - changing the sampling rate based on the received one or more indications.
17. The method of claims 15 or 16, further comprising:
 - generating, by the one or more processors, a trigger signal for synchronizing operation of the flow control device and the sampling rate.
18. The method of any one of claims 11-17, wherein the sampling rate is between 10 Hz and 300 Hz.
19. The method of any one of claims 11-18, further comprising:
 - causing, by the one or more processors, the flow control device to prevent transfer of the liquid during a baseline calibration time interval; and

receiving, by the one or more processors and from the at least one sensor, a baseline value;
wherein computing the indication of fill amount is based at least in part on the received baseline value.

20. The method of any one of claims 11-19, further comprising:
causing, by the one or more processors, the flow control device to transfer the liquid with a constant flow rate during a flow rate calibration time interval; and
receiving, by the one or more processors and from the at least one sensor, a calibration flow value;
wherein computing the indication of fill amount is based at least in part on the received calibration flow value.
21. The method of any one of claims 11-20, further comprising:
determining, by the one or more processors, a start time and an end time of the fill time interval based at least in part on the received plurality of values indicative of the plurality of respective flow rates at the plurality of respective times within the fill-time interval.
22. The method of claim 21, further comprising:
determining, by the one or more processors, and indication of slope in the plurality of values indicative of the plurality of respective flow rates;
wherein determining the start time or the end time is based at least in part on the indication of slope.
23. The method of any one of claims 11-22, wherein the liquid is an injectable therapeutic and the container is configured to contain one or more doses of the injectable therapeutic.
24. The method of any one of claims 11-23, wherein the target fill amount is between 0.2 mL and 40 mL or between 0.2 mg and 40 mg.
25. The method of claim 11, wherein the at least one sensor includes an ultrasonic sensor.
26. The method of any one of claims 11-23, wherein the method further comprises measuring, using a first sensor to measure a first flow rate at a first section of tubing and using a second sensor to measure a second flow rate at a second section of tubing.
27. The method of claim 26, wherein an inner diameter of the first section of tubing is at least 10% bigger than an inner diameter of the second section of tubing.
28. The method of any one of claims 11-27, wherein the at least one sensor includes at least three sensors, and the method further comprises:
determining, by the one or more processors, that one of the at least three sensors generated an outlier measurement;
and
generating, by the one or more processors, an alert based on the outlier measurement;
wherein computing the indication of fill amount is based at least in part on omitting the outlier measurement.

29. The method of any one of claims 11-28, further comprising generating an alert indicating a failure mode or other malfunction.
30. The method of claim 29, wherein the alert indicates dripping, splashing, blockage, and/or an air pocket.