INSTRUMENTATION DEVELOPMENT

Pumps for IVDs: Controlling flow too small to see

A survey of the various types of pumps used in IVD instruments, and a discussion of materials, selection criteria, and purchasing considerations.

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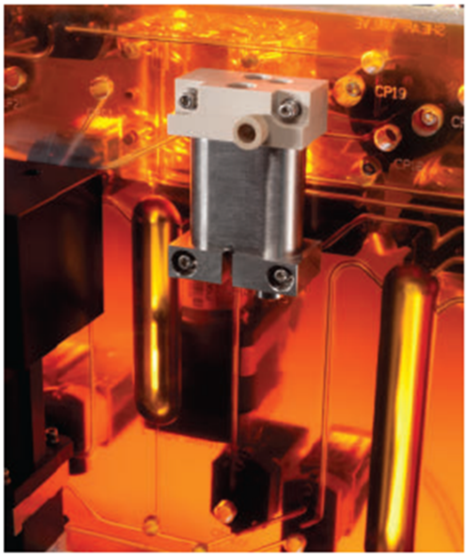

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IVD instruments encompass a broad range of analytical and performance functions, from separation and purification to detection and cell analysis. Many, if not most, of these instruments incorporate fluidic subsystems for sample handling and dilution, and reagent and buffer dispensing, or wash lines to prevent carryover and cross-contamination and eliminate waste fluids.

Depending on the chemistries involved or the purpose for fluidic involvement in the IVD instrument, liquids can range from plain water to acids and bases of varying concentrations. Commonly used compounds include reagents, culture media, control materials, calibration materials, salt waters, surfactants, preservatives, alcohol, and bleach solutions. Even at low concentrations, these compounds can react with the materials from which the system components are made.

Design engineers who are researching fluidic technologies can readily access vast amounts of resources and information that are related to fluid dynamics. However, designers of innovative scientific and IVD instruments that are expanding known boundaries quickly exhaust the published materials relative to fluidic design for the emerging technologies that impel instrumentation development. A fluidic engineer who has spent his career designing IVD instruments has noted, "Information on fluidic development for scientific instruments is almost nonexistent."

To produce a viable and reliable instrument for their customers, designers of IVD and biotech instruments must harmonize a variety of engineering disciplines (e.g., mechanical, electrical, and software) into systems in order to achieve scientific results. In many instances, instrument design involves updates to older machines, and design considerations can confine themselves to improving the performance of legacy systems. Incrementally, however, advancements in science or technology force the development of completely new instruments. At that point, what guides the designer working at a CAD screen and pondering which components to use?

Fluidics is a mechanical discipline. The terms *fluidics* or *fluidic logic* originally described the use of a fluid, pneumatic, or hydraulic medium to control analog and digital operations, similar to electronic control. Over time and use, the terms became broadly synonymous with fluid systems as used in the instrumentation industry. This article reviews the key pump components and systems used in IVD instruments for transferring liquids and the materials that are best suited for each function.

Pumps In IVD Instruments

The heart of any IVD fluidic system is the pump (one or more) that is used to aspirate, dispense, or flow continuously certain volumes of liquids at defined rates (usually very small rates).

Although the broad origins of clinical chemistry date back to antiquity, the rapid development of analytical processes in the 1800s and the further miniaturization of methods and samples in the 1900s enabled the advancement of process automation that continues today. A common challenge for all practitioners (from alchemists to today's clinical chemists) has been the necessary limitation

Figure 1. Otto Folin in the chemistry laboratory at the McLean Hospital (Waverly, MA). As early as the 1930s, specialized laboratories routinely performed tests using only 100 µL of blood serum. (Photo courtesy McLean Hospital.)

of processing small samples, particularly blood. As far back as the 1930s, specialized laboratories routinely performed tests using only 100 µL of blood serum (see Figure 1).

While a design engineer might cerebrally comprehend the mathematical concept of microliters or nanoliters, few truly understand the reality of controlling flow, dispensing liquids, or accommodating viscosities in such infinitesimal amounts. A microliter (µL), which is the most common unit of measure in IVD fluidics, is one millionth of a liter. A nanoliter, which is rapidly becoming the preferred volume, is one billionth of a liter (see Figure 2). A single drop of water at room temperature is approximately 50,000 nL. When that volume range is narrowed by a time requirement (e.g., 5 nL dispensed during a minute or an hour), a designer whose formulas originally calculated flow in pipes at gallons per minute is in new territory. In addition, at micro and nanoflow rates, known properties of fluid dynamics (e.g., turbulence and mixing) can change dramatically.

Selecting a pump for a next-generation IVD instrument that can process 2000 minute human samples every hour demands exceptional performance specifications for accuracy and precision. Although these terms are often used interchangeably, for the purpose of this article, *accuracy* is defined as the relationship between a target delivery volume and the actual volume delivered. For example, in a pump that is set to dispense 100 µL, if 98 µL is actually delivered, the accuracy rating of the pump is 98%, or it registers a 2% error. Meanwhile, *precision* measures the repeatability or average accuracy of a group of dispenses, and is expressed by a coefficient of variation (CV), which is the standard deviation of a number of dispense events divided by the mean value of those dispenses. For example, at a dispense rate of 100%, the error average, or CV, is less than 0.2%.

A number of other factors also influence pump component selection and overall IVD instrument design, including the following:

Flow rate. Typical sample volumes may range from 1 to 30 µL, and typical reagent volumes from 25 to 300 µL. Bulk liquids might flow at 1-5 milliliters/min.

Fluid characteristics. For liquids that are commonly encountered in IVD instruments, the following characteristics should be taken into account. First, liquid type. Some liquids can precipitate abrasive salts or other particulates that accumulate inside a pump head and shred pump seals. Other fluids may clot, creating obstructions and volume anomalies. The second characteristic is viscosity. Most calculations could reliably use the viscosity of water as a standard. However, in hematology, whole blood (a non-Newtonian fluid) does not adhere to Newton's viscosity law, which describes constants in flow properties of certain fluids. Temperature is the third characteristic. In general, most IVD reactions occur at body temperature (37° C) in a reaction chamber or incubator. Reagents are usually refrigerated in compartments with a range of 4 to 10° C.

Chemical compatibility. Can seals, pistons, pump bodies, pump heads, and other wetted parts withstand continuous, long-term contact with circulating liquids?

Pressure/Back pressure. Working pressures in IVD instruments rarely exceed 100 psi or 6.9 bar.

Speed per increment of aspiration/dispense. How fast must a pump supply the designated volumes in order to achieve the targeted results (e.g., 2000 tests per hour) or potentiate time-sensitive chemistries?

Backlash compensation for precise positioning of the moving parts of a

Figure 2. Straightforward microfluidic calculation illustrates the Lilliputian world of microflow. At microflow rates of 1 µL/min, an emerging flow rate for IVD instruments, emptying the contents of a standard wine bottle (750 mL) would require 1.42 years. At nanoflow rates, that length of time jumps to 1420 years.

pump. Pumps that are chosen for high accuracy and precision should compensate for backlash, or the amount of motion and accuracy that could be lost if the motion range of a pump exhibits slack when motion reverses. This might be seen as the amount of clearance between mated gear teeth.

Operating environments for the media pumped, the ambient conditions within an IVD instrument, and even temperatures encountered in shipping. System operating temperatures usually range from 18° C and 20% relative humidity to 30-32° C and 90% relative humidity. Shipping and storage temperatures may range from -40° C to 40° C.

Life cycle describes how many cycles a pump can run during its life span. The ideal situation is a component that will last an IVD instrument's entire life span without any failures and little or no maintenance. Once on the market, an instrument's lifespan could be 5 to 7 years or longer. An engineer evaluating a pump rated with a five-million-cycle life span matches that rating to the calculation that five million cycles will operate in an instrument for three years. The engineer will then schedule field service or an overhaul of the pump during a system maintenance check.

Electrical requirements affecting global instrument distribution, motor type, and current usage should comply with local regulatory standards.

Size. A fluidic system's overall footprint relative to the target dimensions of the IVD instrument for benchtop and floor-style systems.

Connections. How the pump supplies liquid to other parts of the fluid circuit. Connection options include tubes and fittings or manifold assemblies. Each point of fluid connection creates an opportunity for a potential leak. In IVD systems, leaks can be very destructive to other subsystems, such as electronics. Leaks can also compromise test results with erroneous readings.

Figure 3. The Sapphire Engineering VP17, a piston dispense pump by IDEX Health & Science. (Photo used by permission.) Other piston dispense pumps for IVD instruments are made by The Lee Co., Kloehn, and others.

Self-priming, suction lift, and dry running capabilities. Enabling an IVD system to run with little or no operator intervention enhances the reliability of the system and saves money on maintenance and operation.

Cost of a pump relative to the cost constraints of an IVD instrument's development. In recent years, in response to clinical laboratory trends, IVD instruments have become more multiplexed and sophisticated, and instrument companies have consequently diversified and adapted their selling strategies. By moving away from a leasing model with low entry costs while balancing higher operating costs, today's instrument suppliers are more likely to set a higher selling price to recoup a system's development costs. This shift has placed enormous pressure on technology designers to reduce the costs of developing instruments at every stage, while continually increasing their performance to outpace emerging competitors in China and India. In addition, during the recession, laboratories and hospitals allocated fewer dollars for capital expenditures and operating costs, creating additional cost-saving imperatives.

Pump Technologies

A quick Internet search for pump technologies brings up a wealth of information on various Web sites, such as Pump School courtesy of Viking Pumps or the Pump Guy with seminars from the Flow Control Network. Filtered by function, the vast pump universe can be narrowed down to three subgroups that are differentiated by key performance targets. Each subgroup is examined separately here. High-precision dispensing pumps provide accuracy, precision, and variable flow for chemistries such as sample and reagent interactions. Dispensing or metering pumps work well in IVD systems that require accurate, reproducible, and fixed volumes of fluids, including some reagent handling and wash systems. Motor-operated metering pumps provide continuous, stable, and low-cost fluid handling for bulk reservoirs and wash systems.

High-Precision Dispensing Pumps

Piston dispense pumps incorporate a piston assembly in a high-precision machined body, with an optional seal wash that prevents salt-crystal formation and prolongs the life of the seal and pump head (see Figure 3). A

Figure 4. The TriContinent C3000 syringe pump. (Photo used by permission.) Other syringe-style pumps for IVD instruments are made by Hamilton Co., Kloehn, Tecan, and others.

stepper motor that is connected to a lead screw drives the piston during the aspirate and dispense cycles.

The wetted parts in high-precision dispensing pumps are the head, piston, and seals. The pros of these pumps include very high accuracy (within 99.5%), high precision, variable aspirate and dispense volumes, and elimination of the need and cost of routine syringe replacement. The cons can include a low seal life (without a seal wash).

Syringe pumps are positive-displacement piston pumps consisting of a syringe (typically 30-60 millimeters in length) that is mounted to a drive mechanism. The drive mechanism can be operated by a DC servo or stepper motor with a direct-drive or belt-driven lead screw that can be backlash-compensated to increase repeatability. The drive actuator moves the piston rod in and out of the syringe in cycles for aspirating and dispensing liquid. Standard syringe volumes range from 25 µL to 5 mL in varying increments, from which lower, variable volumes can be dispensed repeatedly (see Figure 4).

Figure 5. The solenoid-operated diaphragm pump by The Lee Company. (Photo used by permission.) Other diaphragm pumps for IVD instruments are made by Bio-Chem, Bürkert Fluid Control Systems, SMC, KNF-Neuberger, Takasago, and others.

The wetted parts in syringe pumps are the syringe piston and rod, barrel, seals, and port (if applicable). The pros of these pumps include very high accuracy (within 99.5%), high precision, and variable aspirate and dispense volumes. The cons are their high costs, the routine service needed to replace syringes or seals, and a low pump life.

Dispensing and Metering Pumps

Solenoid-operated diaphragm pumps are often implemented in IVD instruments for dispensing a wide variety of fluids at set volumes per cycle of the solenoid (see Figure 5). For example, this type of pump may be used to dispense certain reagents and wash solutions with a lower requirement for accuracy. The volume set-point of the solenoid defines the volume per cycle. Varying the speed of the pump stroke changes the total volume dispensed.

The wetted parts in dispensing and metering pumps are the diaphragm, pump body, and check valves. The pros of these pumps include a high cycle life, a broad choice of wetted parts that are suitable for IVD applications, lack of noise, self priming, and system integration aided by manifold mounting. The cons are an accuracy of only 95-97% per cycle, a required chemical compatibility with major pump parts, and a fixed, nonvariable dispense per cycle.

The low cost and simple operation of peristaltic pumps make them an attractive choice for many simple metering and dosing applications in IVD and biotech instruments (see Figure 6). Liquid in a peristaltic pump never touches the pump mechanism because it travels through flexible tubing. Positive displacement forces the liquid through the tubing as rollers rotate against the tubing, squeezing it against the pump housing. As the rollers move on, thereby releasing the tubing, it expands to allow more fluids to enter. During this operation, at least one roller compresses the tubing at all times, preventing backflow and eliminating the need for control valves.

Figure 6. The Ismatec MS/CA peristaltic pump by IDEX Health & Science. (Photo used by permission.) Other peristaltic pumps for IVD instruments are made by Barnett, Brandle, Instec, Masterflex, Watson Marlow, Cole Parmer, and others.

The only wetted part in peristaltic pumps is the tubing. The pros of these pumps include the ease of cleaning and maintainance; their low costs; the availability of multichannel flow; the ability to pump solids, viscous, or aggressive liquids; and the low cost of tubing. The cons are the varying degrees of pulsation (even with multiple rollers), variable accuracy and precision depending on the tubing materials and wear, and tubing maintenance.

In oscillating piston pumps, liquids move by the synchronous rotation and reciprocation of the ceramic piston in the precisely mated ceramic cylinder liner. One complete piston revolution produces each suction/discharge cycle. By design, the piston always returns to the cylinder bottom for maximum fluid displacement and bubble clearing. Oscillating piston pumps are manufactured by Diener Precision Pumps Ltd. (Embrach, Switzerland), Fluid Metering Inc. (Syosset, NY), IVEK Corp. (North Springfield, VT), and others.

The wetted parts in oscillating piston pumps are the ceramic piston, cylinder liner, and housing. The pros of these pumps include an accuracy of ±1%, a precision of 0.5% CV, the elimination of flow-control valves, self-priming, simple construction, only one moving part (the piston), and reversibility. The cons are an awkward design, susceptibility to particulate contamination, no onboard wash system installed, and the inability to manifold-mount discrete, free-standing pumps.

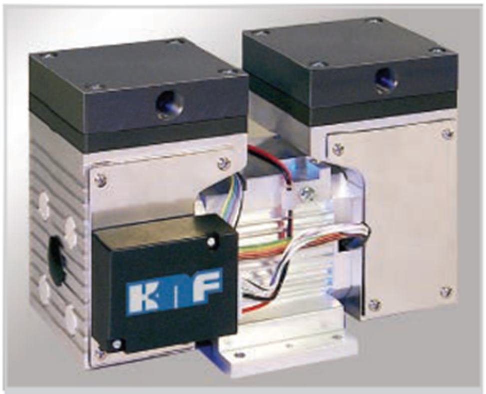

Figure 7. The KNF-Neuberger N838.0 motor-operated diaphragm pump. (Photo used by permission.) Other motor-operated diaphragm pumps for IVD instruments are made by Thomas, Hargraves, and others.

Motor-Operated Metering Pumps

In motor-operated diaphragm pumps, which are reciprocating pumps, a connecting rod moves the flexible diaphragm into the pump head guided by an eccentric on the motor shaft (see Figure 7). The downstroke draws the fluid into the pump chamber, and the upstroke expels the fluid from the chamber. One-way valves control the direction of the flow.

In motor-operated gear pumps, two or more rotating gears mesh together (see Figure 8). Power from the motor turns one of the gears, which in turn drives the other gears. The spaces between the gear teeth carry the fluid from the inlet to the outlet. The gear mesh point prevents the fluid from returning to the inlet, eliminating backflow issues. The gear pumps are pulsation-free and are preferred in applications requiring flow stability.

In motor-operated centrifugal pumps, an eccentrically positioned rotor within the pump cylinder moves counter-clockwise around the interior of the cylinder. When the rotors turn, rotor blades fit into numerous rotor slots. Centrifugal force throws the

Figure 8. The Micropump GA-series gear pump by IDEX Health & Science. (Photo used by permission.) Other gear pumps for IVD instruments are made by Gorman-Rupp, Diener, and others.

blades out in a line that slides against the internal surface of the cylinder. The constantly moving rotor draws in air or liquid through the inlet, trapping it in a cell between the two blades on a line that continually changes with the rotation. This fluid fills the cell until the rear blade reaches the inlet port and the cell has achieved maximum volume. As the cell moves away from the port, its shrinking internal volume compresses and displaces the air or liquid in the cell. This process continues until the pressure in the cell exceeds that in the pressure chamber, forcing the air or liquid to exit through the outlet port. Centrifugal pumps for IVD instruments are manufactured by Gorman-Rupp Co. (Mansfield, OH), Iwaki America Inc. (Holliston, MA), and Schwarzer Precision GmbH (Essen, Germany), and others.

The wetted parts in motor-operated metering pumps are the pump housing and cylinder, diaphragm, valves, check valves, gear head, rotor, and vanes. The pros of these pumps include their lower costs, high flow, compactness, and low vibration. The cons are a lower accuracy, as low as 90%.

The Future of IVD Instruments

The consensus among IVD instrument designers and component providers is that the key trend guiding system design during the next five years will be the drive toward miniaturization and minimizing costs in order to maximize the cost per test for the customer. Systems must require less design time, making them cheaper to build. Most importantly, instruments will use smaller reagent volumes, demanding ever-smaller flow paths with a functional limit of 0.0020" before higher system pressures and temperatures interfere. IVD

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