

Application of Disposable Pressure Sensors to a Postcentrifugation Filtration Process

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Understanding the performance of filtration unit operations in the processing of therapeutic agents is important. Incorrect or misunderstood filter performance can significantly affect the efficiency and operation of many other unit operations in a bioprocessing train. Ultimately the cost of goods will suffer significantly without adequate process characterization. Therefore, the methods and tools used to screen and size filters in a cost effective, practical, and operationally friendly manner are central to any development function. Many aspects of the well-publicized disposable bioprocessing philosophy lend themselves particularly well to the high-throughput screening of filter types and the sizing of filters at development scales for use in scale-up models.

Although no viable single-use centrifugation option has yet arisen, one specific application in which disposables are appropriate is centrifugation harvest development. Development of traditional centrifuge processes for removal of cells and cellular debris varies by such parameters as cell viability and concentration or packed cell volume (PCV), feed flow rate, and bowl speed. However, the input operational parameters of a centrifuge process directly affect the filterability of the output concentrate. Process analytics such

as sedimentation profiles and measurements of turbidity, although extremely important to process development and characterization, are insufficient for determining operational set points or understanding the resulting cost for goods of filter use.

Arguably, the most appropriate method of modeling process performance for cell-removal unit operations is through measuring the capacity of depth and sterile filters downstream of a centrifuge as a function of its operating conditions (bowl speed and flow rate) and the filter types. Pressure is a critical parameter to measure as an indication of filter performance and capacity. Performing such a multiple-factor experiment (including bowl speed, flow rate, and filter size, type, and manufacturer) can produce a large number of conditions depending on the experimental design strategy (Figure 1). Implementing systems and equipment for filtration screening is therefore critical to executing a successful development study. Important factors to consider when implementing numerous filtration studies include data collection, storage and analysis; operations monitoring; and repeatability.

With pressure as a key dependent variable in such experimentation, pressure data collection is an important feature of any system design. Traditional pressure gauges require intensive operator monitoring,



Photo 1: Pressure sensors with Luer inlet/out (www.pendotech.com)

cleaning, inconvenient calibration procedures, and data collection and transcription. Because stainless steel sanitary pressure transducers can be difficult to adapt to small-scale flexible tubing, adapters, gaskets, and clamps, a sanitary tee (with undesired hold-up) may be required. It would be advantageous to integrate a disposable pressure sensor into the vent hole or feed line of a screening miniature filter capsule that can be calibrated easily (or that doesn't require calibration), disposed of cheaply, and (most important) integrated with a data collection and retrieval system.

A SINGLE-USE OPTION

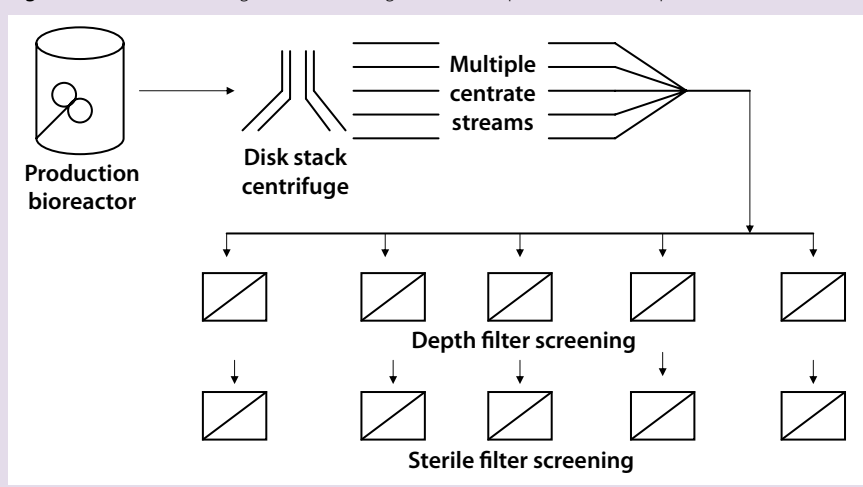
Disposable pressure sensors with narrow flow-through paths (~0.0625-in. ID) and Luer fittings on their inlet and outlet can facilitate small-scale process development

studies such as the harvest development process step described above. These sensors come with a 12-in. disposable cable that connects to a reusable cable that is in turn connected to a monitor. For small-scale processes, they can be used with flexible tubing in flow-through mode by adding hose-barb-to-Luer adapters. Particularly with small tubing IDs, those are useful because connecting traditional pressure measurement devices into a process stream can be difficult. A tee fitting with a Luer port should be used for wider flow paths (e.g., 0.25-in. ID) because the sensor works in dead-end mode (Photo 1).

Depending on the type of filter used, a sensor can be connected directly to a filter vent port to measure pressure. At laboratory scales, Luer fittings are proven to work well and allow easy adaptation of experimental setups. They can be used with three-way or four-way valves that have Luer ports for optimal flexibility. In flow-through mode, hold-up volume and fluid path obstructions are eliminated. With sensors used on tees or filter ports, testing has indicated accurate measurements at a wide range of flow rates.

There is an increasing trend in the industry toward use of disposables (e.g., flexible tubing and disposable bioprocess containers) in both clinical and commercial production to about the 1,000-L process scale. Monitoring pressure in general leads to process consistency and better understanding of, for example, a harvest process in development. New disposable pressure

Figure 1: Process flow diagram for centrifuge and subsequent filter development



sensors from PendoTECH are optimized for large-scale process monitoring and small-scale process screening.

These sensors are embedded at the interior wall surface of fittings that are similar to hose-barb connectors (Photos 2A and 2B) and are available to accommodate from 0.375-in. to 1-in. ID tubing. Using disposable sensors at process scales eliminates the requirements of parts cleaning, tracking, sanitization, and possible reesterilization of reusable pressure measurement devices. The ability to use 1-in. tubing gives a flow rate potential of 50 L/min or more for production applications. An unobstructed flow path without dead-legs minimizes pressure drops associated with pressure measurement devices. That's important because as filters clog and flow rates change, a minimal ΔP (pressure drop across the filter) contributed from the device will affect data collected (Photo 3).

At larger scales, sensors with hose-barb inlet/outlets are a better choice. Luer fittings run the risk of being dislodged and may not be optimally adopted to a process set-up. Also, process-scale sensors can be used in situations where barb connectors may otherwise be used anyway, such as transitioning from one type of tubing to another. The hose-barb design is a proven one from Eldon-James Corporation (www.eldonjames.com), a manufacturer of plastic fittings that are used on many existing bioprocess assemblies. The design eliminates mold-parting lines (which can contribute to leaks) where tubing is secured. The single barb shaft provides space for a hose to relax behind the barb, causing the tie-wrap to function like a drawstring. A tie-wrap placed over the exclusive antirotation device (patented by Eldon-James) will lock the tubing, preventing it from being freed by any twisting motions.

Photo 2: Large-scale sensors with hose barb inlet/outlet; (A) pressure sensor device, (B) device installed

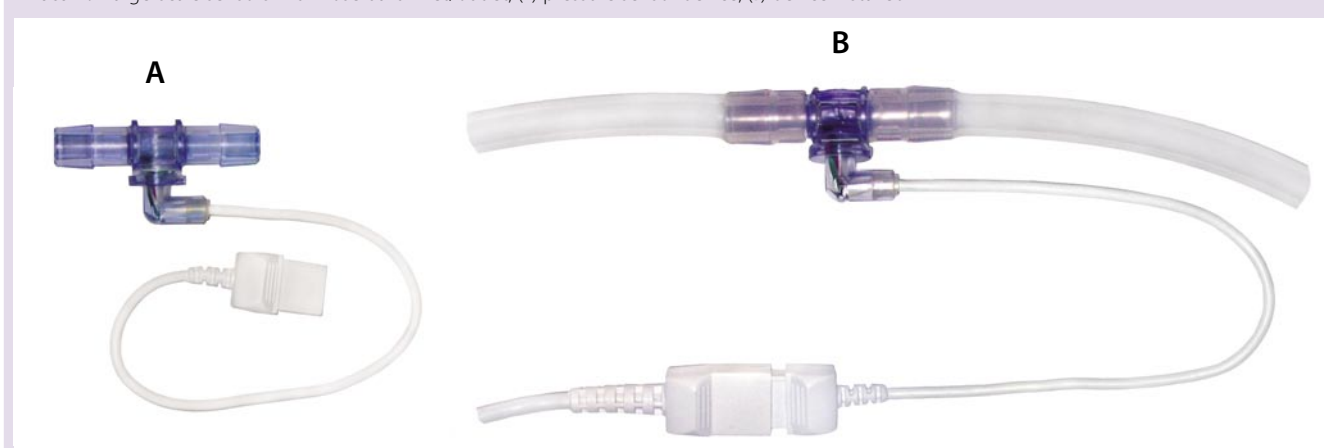




Photo 3: Large-scale pressure sensor flow path (WWW.PENDOTECH.COM)

MICROELECTRONICS FOR BIOPROCESSING

At the heart of this technology is a low-cost MEMS (micro-electro-mechanical system), which is the integration of micromachined mechanical elements, sensors, actuators, and electronics on a common silicon substrate through microfabrication technology (1). These pressure sensors are manufactured using a silicone, micromachined, piezoresistive sensing element in a Wheatstone bridge circuit, in which an applied pressure to the circuit induces a proportional output voltage. Previous testing of such MEMS pressure sensors on silicone chips yielded very positive results with respect to accuracy, repeatability, and robustness that would be required for bioprocess applications (2).

The material used to mold the plastic part of these sensors is a polycarbonate that meets USP Class VI tests and is compatible with gamma-radiation and ethylene oxide chemical sterilization methods. Before installation into finished devices, the chips undergo integrity testing that includes a pressure test to >100 psi. Each individual finished device undergoes several tests for electrical integrity, to confirm the absence of

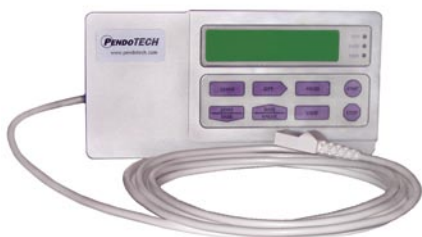
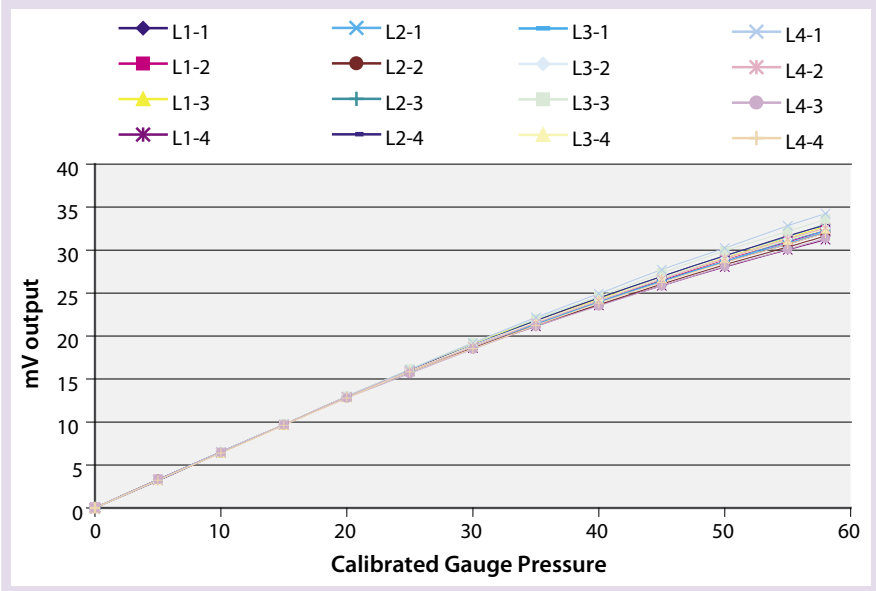


Photo 4: PressureMAT sensor (WWW.PENDOTECH.COM)

Figure 2: Disposable pressure sensor data (millivolt output compared with pressure) using four sensors from four lots



leaks, and to ensure proper calibration within a tight specification range. If they do not meet release criteria, they are rejected from production.

The sensors give an output of 0.2584 mV/psi/V up to about 30 psi. Beyond that point, the sensor output is nonlinear, so a polynomial calibration has been determined to account for that. With many depth filtration processes, particularly when tubing and peristaltic pumps are used, it is desirable to keep operation pressures below 20–22 psi to prevent breakthrough of cells and cell debris as well as to prevent tubing rupture. Sensor accuracy is better than ± 0.3 psi up to 15 psi and $\pm 2.5\%$ of the reading

value from 15–22 psi (Figure 2).

The circuit in these pressure sensor chips requires a narrow range of applied voltage, and the applied voltage to these circuits gives a voltage output directly proportional to pressure. That signal is not a traditional field output signal such as 0–20 mA or 0–10 V. Along with the requirement of data output to a data collection and retrieval system (e.g., a SCADA system for data acquisition and process control or a simple PC), this necessitates an intermediate device. PendoTECH offers two systems for this purpose: PressureMAT and PendoKIT.

Figure 3: Cell harvest application with disposable sensors

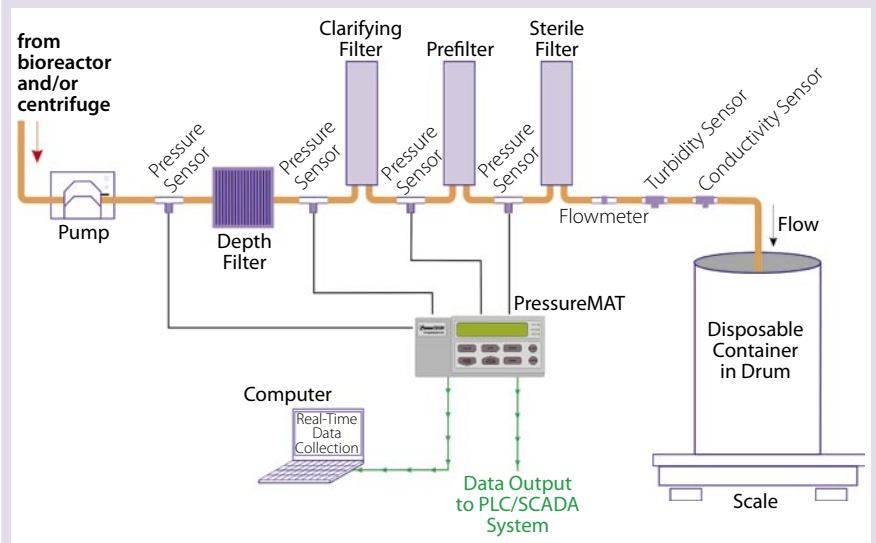
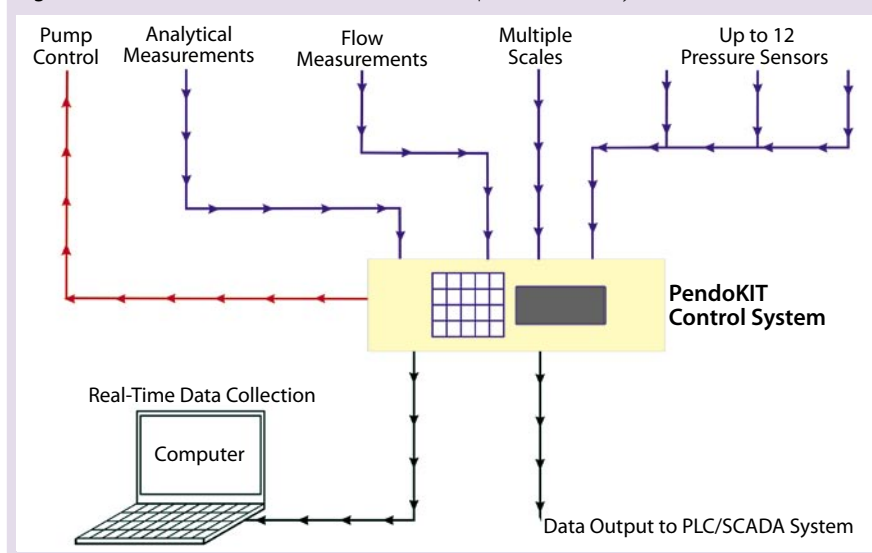


Figure 4: Process data collection with the PendoKIT process control system



PressureMAT is configured for one to four disposable pressure sensor inputs. It displays the pressure values, can transmit those to both a PC (RS232 output) and a process control system (4–20 mA output), and has an alarm based on user-entered minimum and maximum set points with dry-contact relay outputs (Photo 4). Operation is simple: A sensor is installed with a 12-foot reusable cable and, at atmospheric pressure, the auto-zero button on the control panel is pressed. This device is ideal for collecting data in multistage depth filtration processes (Figure 2).

The PendoKIT custom-configurable process control system can handle up to 12 pressure sensors as well as other options such as scale inputs, pump speed control, and on/off controls as well as 4–20 mA outputs, alarm outputs, flowmeter inputs, pinch valve outputs, process analytical sensors, and others (Figure 3). This system also features real-time process data acquisition to a PC directly (with software such as Excel) or to a PLC/SCADA system. For example, for a cell harvest application, a PendoKIT system can be configured with flowmeters and scale inputs for process monitoring and data acquisition (Figure 4).

IMPROVING PROCESS KNOWLEDGE

Process analytics are critical to understanding the limits of all bioprocesses. Implementing reliable,

robust, and operationally friendly systems and methodologies for performing process development and monitoring manufacturing processes always improves process knowledge. Including disposable technologies provides a unique opportunity for the addition of an operationally friendly system that sacrifices none of the analytics that are critical to a process.

ACKNOWLEDGMENT

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