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# Suitability of Select In-line Single-Use Sensors for PAT in Continuous Processing

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## Abstract

The requirements for batch versus continuous processing are compared along the lines of the design attributes of single use sensors for pressure, temperature, conductivity, UV absorbance, and a new low flow sensor and also performance over months of continuous operation. These sensors are applicable in both upstream and downstream processing starting with monitoring on single use bioreactors, sensors required for perfusion process monitoring followed by monitoring of continuous purification processes. Points of consideration are the materials used and their durability for extended use beyond a batch process, availability of sensors for low flow rates often used in continuous processes, performance in terms of a sensor remaining in calibration over an extended run, Finally, during continuous processing, it is often imperative that a process can be continuously controlled and data can be logged and trended 24/7. Therefore, interface of the sensors to higher level control systems and to data historians is important and options will be examined to accomplish this for different plant architectures.


## Introduction

For the single use sensors, design attributes in terms of material durability and smaller sizes than traditionally used in batch process is important. Dissection of the materials of the sensors and their physical nature to withstand liquid exposure of up to 90 days versus (versus shorter more discrete batch processes of less than one day) will be examined on the core material basis. Lower flow rates will be used in some instances for continuous processing versus rapid batch process so it is desirable to have a robust sensor that adapts to 1/8 inch inner diameter tubing. With single use sensors, calibration can often not be done at the time of use because of the closed nature of the bioprocess system. How the both the sensors and their corresponding monitors can meet the requirement of "no calibration required" at the point of use will be presented which is an important aspect in single use systems for continuous bioprocessing. In addition to examining impact of time and type of exposure of the sensor materials, during a continuous process of up to 90 days, the susceptibility to sensor measurement drift / change in calibration over time will be examined. Finally, during continuous processing, it is often imperative that a process can be continuously controlled and data can be logged and trended 24/7. Therefore, interface of the sensors to higher level control systems and to data historians is important and options will be examined to accomplish this for different plant architectures.

## Single use sensor type materials and sizes/technology

For extended continuous processes (versus a batch/discrete process), single use sensors made of materials that cost less than traditional stainless steel instruments, must stand the test of time and not degrade which would lead to a host of issues in the process. Of course, initial qualification analysis would lead to any potential chemical compatibility issues and sensors with material compatibility issues should be avoided. The materials used in the sensors presented here are manufactured of mostly polymeric materials that are designed to last many years and are used in many consumer products with this attribute required. Figure 1 lists the materials used and they are all durable and used in other products where the material is design to last many years. Also listed is the sensor method that enables to be used without direct user calibration at the point of use.

Figure 1. Robust Materials for Use Over Extended Time Periods

| | Pressure | Temp. | Conduct. | Absorb. | Low Flow Meter |
|---|---|---|---|---|---|
| **Main contact material** | Polysul-phone or Polycarb-onate | Polysul-phone | Polysul-phone | Polysul-phone | Polyether-imide (PEI) |
| **Other(s)** | Dielectric silicone; Adhesive | Stainless steel; Adhesive | Stainless steel; Adhesive | Quartz glass (fused silica) | Liquid-Crystal Polymer (LCP); Adhesive |
| **Built-in Accuracy Method** | Manufactured to tight tolerances; 100% testing | Manufactured to tight tolerances; 100% testing | K determined after manufacture | Tight tolerances on molded part to fix the path length | Fully calibrated; temperature compensated |

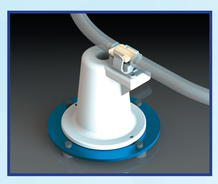
For low flow management in continuous processing, 1/8 inch ID tubing is frequently employed into a process and sensors optimized for this size are required. For low flow rates (ie, < than 15mL/min) the smaller ID will maintain a liquid velocity to prevent settling and keep the fluid streaming moving so it remains uniform. Figure 2 presents a table of sensors either available or under development and technological challenges for development. Since conductivity is often needed to be measured in a storage container, a port plate for a bag is under development. Figure 3 shows pictures or renderings of these sensors.

Figure 2. Sensors for 1/8 inch ID Tubing - Status of Availability and Key Issues

| | Pressure | Temp. | Conduct. | Absorb. | Low Flow Meter |
|---|---|---|---|---|---|
| **Status** | Available | Under Development | N/A ^ | Under Development | Under Development |
| **Issues** | Molding of small part | Molding of small part | -- | Molding of small part, assembly | Different technology required versus higher flow measurement |

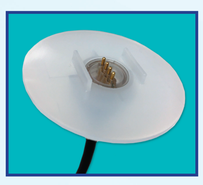
^ for continuous processing, probes for vessels and bags under development as priority

Figure 3.

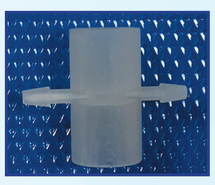


Flow

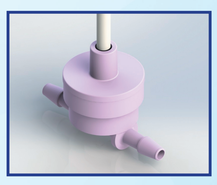
Pressure



Conductivity for Vessel



UV



Temperature

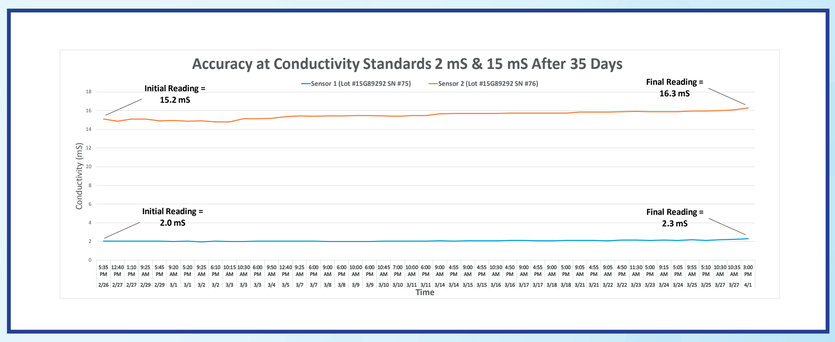
## Performance

The growth of continuous processing in bioprocessing coupled with the benefits of single use technology (SUT) creates demand for SUT sensors that have proven performance in long term use. To demonstrate the performance of SUT sensors over time, laboratory studies on PendoTECH Single Use Pressure Sensors™ and also on SUT conductivity sensors were carried out to provide data showing that the sensors will maintain their accuracy in continuous use. In a related study, the long term stability of PendoTECH UV/Vis/NIR photometer was determined and is reported here. And initial testing on a new flow meter for use in the range of 0.5 to 10mL/min was conducted. Many of the flow measurement technologies used to measure higher flow rates like ultrasonic, Coriolis, magnetic, rotary are difficult to miniaturize and/or are too expensive to be used as a single use technology. A new flow meter with a chip-based heat capacitance flow measurement principle (core sensor offered by Sensirion) is under development. Initial testing involved performance measurement and also compatibility with bio-burden reduction treatments (Ethylene Oxide, Autoclave and Gamma) and hence measurement post-treatment.

### PendoTECH Single Use Conductivity Sensors

A 35 day static continuous laboratory test was carried out on PendoTECH Single Use Conductivity Sensors™ to provide data demonstrating that the sensors will maintain their accuracy in long term use.

Figure 4.




Conclusion:

While a slight drift upward in readings was noted over 35 days, it is clear that the solutions used in this 35 days test study experienced an increase in concentration, very likely due to some evaporation of water during the test. Taking that into consideration, the conductivity sensors showed no change in reading over 35 days at ambient temperatures.

### PendoTECH Single Use Pressure Sensors

To demonstrate the long term accuracy of PendoTECH Single Use Pressure Sensors a 93-day experiment was carried out: 93 days with constant pressure of 10 psi. Figure 5 summarizes the data from the 93-day period. Figure 6 displays the post-experiment testing with a calibrated gauge (with no tare conducted post-experiment).

Figure 5.

**Accuracy at Constant 10 psi After 93 Days**

| * = Polysulfone | Test Duration: 10/25/2016 - 1/26/2017 | | | |
|---|---|---|---|---|
| **Sensor ID** | **Average Pressure (psi)** | **Minimum Range (psi)** | **Maximum Range (psi)** | **Sensor Performance** |
| 1152607-01 | 10.03 | 9.94 | 10.12 | Pass |
| 1152607-02 | 10.01 | 9.92 | 10.10 | Pass |
| 1152607-03 | 10.00 | 9.91 | 10.09 | Pass |
| 1152607-04 | 9.93 | 9.85 | 10.04 | Pass |
| 1161066-01* | 10.02 | 9.95 | 10.11 | Pass |
| 1161066-02* | 10.01 | 9.94 | 10.11 | Pass |
| 1161066-03* | 10.04 | 9.97 | 10.15 | Pass |
| 1161066-04* | 10.01 | 9.93 | 10.09 | Pass |
| 1151819-01 | 9.99 | 9.88 | 10.08 | Pass |
| 1151819-02 | 10.00 | 9.89 | 10.10 | Pass |
| 1151819-03 | 10.01 | 9.90 | 10.11 | Pass |
| 1151819-04 | 10.01 | 9.91 | 10.10 | Pass |
| **Acceptance Criterion (+/-)** | 3% 0.30 | 3% 9.70 | 3% 10.30 | **All Within Specifications** |

Figure 6.

**Pressure Accuracy Verification Post 93 Days**

| * = Polysulfone All others = PC | Test Duration: 10/25/2016 - 1/26/2017 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sensor ID** | Applied Pressure (psi) | | | | | | | | **Sensor Performance** |
| | 0 | 5 | 10 | 20 | 30 | 40 | 50 | 60 | |
| 1152607-05 | -0.03 | 4.99 | 10.10 | 20.17 | 30.09 | 40.29 | 50.58 | 61.09 | Pass |
| 1152607-06 | -0.04 | 4.97 | 10.05 | 20.19 | 30.09 | 40.56 | 51.22 | 62.15 | Pass |
| 1152607-07 | -0.04 | 4.95 | 10.08 | 20.22 | 30.21 | 40.85 | 51.78 | 62.99 | Pass |
| 1152607-08 | -0.05 | 4.93 | 10.01 | 20.05 | 30.10 | 40.49 | 51.52 | 62.67 | Pass |
| 1161066-05* | -0.02 | 4.99 | 10.07 | 20.20 | 30.15 | 40.48 | 51.29 | 62.17 | Pass |
| 1161066-06* | -0.03 | 4.99 | 10.07 | 20.19 | 30.13 | 40.50 | 51.26 | 62.14 | Pass |
| 1161066-07* | -0.02 | 4.99 | 10.13 | 20.19 | 30.28 | 40.72 | 51.33 | 62.32 | Pass |
| 1161066-08* | -0.03 | 4.98 | 10.07 | 20.12 | 30.17 | 40.41 | 51.11 | 61.93 | Pass |
| 1151819-05 | -0.01 | 4.98 | 10.03 | 20.12 | 30.17 | 40.46 | 51.26 | 62.14 | Pass |
| 1151819-06 | -0.04 | 4.98 | 10.09 | 20.14 | 30.16 | 40.67 | 51.35 | 62.29 | Pass |
| 1151819-07 | -0.03 | 5.00 | 10.10 | 20.16 | 30.18 | 40.72 | 51.44 | 62.52 | Pass |
| 1151819-08 | -0.01 | 5.00 | 10.06 | 20.19 | 30.27 | 40.72 | 51.44 | 62.42 | Pass |
| **Acceptance Criterion (+/)** | | 2% 0.10 | 3% 0.30 | 3% 0.60 | 3% 0.90 | 5% 2.00 | 5% 2.50 | 5% 3.00 | **All within specifications** |

Conclusion:

After 93 days exposure to 10 psi the pressure sensors remained accurate.

Overall, the test results clearly show the PendoTECH Single Use Pressure Sensors remain well within their stated accuracy specification over the life of the experiments.

### PendoTECH UV/VIS/NIR Photometer

The PendoTECH UV/Vis/NIR system consists of a photometer with wavelength specific LED light source, fiber optic cables and optical couplers, and flow cell. Figure 7 summarizes the data at the end of the experiment as measured with standards with no base-line tare conducted post-experiment.

Figure 7.

**Accuracy of 280 nm UV Photometer After 93 Days**

| Test Duration: 10/25/2016 - 1/26/2017 | |
|---|---|
| **280 nm Standard** | **UV (AU)** |
| 0.46 AU Standard | 0.45 |
| 1.01 AU Standard | 0.99 |
| 1.51 AU Standard | 1.50 |
| > 2.00 AU Standard | 2.03 |

Conclusion:

After 93 days powered on and in-service, the PendoTECH UV transmitter continued to test within specifications for the entire output range of the unit.

### Low-Flow Flowmeters

A new low flow meter from Sensirion was tested by PendoTECH for its performance in its specified range of 0.5 to 10mL/min. The accuracy claim is an absolute +/- 0.042mL/min up to 0.83mL/min then +/- 5% of reading above that. A custom sensor holder and reader was designed by PendoTECH for the testing. Twenty-five sensors were tested and exact flow rates were not able to be generated but they could be measured independent of the sensor and compared to the sensor reading. Five ranges were targeted from the low end to the high end and the results are summarized in Figure 8 and data table from one sensor is shown in Figure 9.

Figure 8.

Average values from across all sensors

| Measured Flow Rate (mL/min) | Actual Flow Rate (mL/min) | % Error |
|---|---|---|
| 0.55 | 0.54 | 3.31% |
| 1.02 | 1.01 | 3.10% |
| 3.89 | 3.87 | 1.31% |
| 6.29 | 6.28 | 1.05% |
| 10.19 | 10.14 | 0.94% |

Figure 9.

Serial Number - 172100287

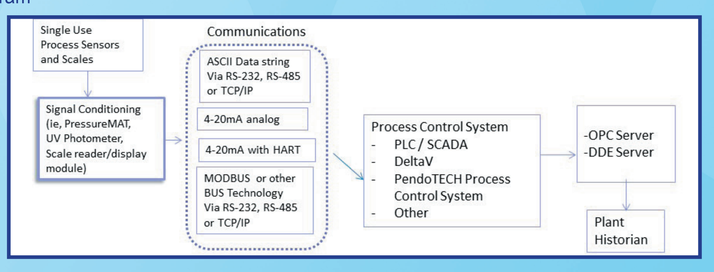
| Measured Flow Rate (mL/min) | Actual Flow Rate (mL/min) | % Error |
|---|---|---|
| 0.60 | 0.58 | 2.6% |
| 1.11 | 1.09 | 2.1% |
| 4.00 | 3.98 | 0.4% |
| 5.99 | 5.88 | 1.8% |
| 10.28 | 10.17 | 1.1% |

Conclusion: All of the 25 sensors tested were within their performance specification. The initial testing of compatibility with ETO and autoclave processing and testing after the processing indicated no impact on performance. Extended process experiments were not completed yet to test continuous use. Custom hardware and software is required to read and integrate this sensor.

## Integration to higher level process control systems

Sensors and their associated monitors ideally have communications capability for higher level control systems and data historians. Analog signals are still popular due to their simplicity but digital technologies are gaining prominence. Figure 10 illustrates a generic architecture diagram and the sensors and monitors occupy the boxes to the left and if the monitors have transmission functions, they can be seamlessly integrated to existing plant architectures.

Figure 10. Integration Diagram




Conclusion: Monitors such as those offered by PendoTECH have communication options for integration to plant architectures. They also have verification tools to test their performance independent of the sensors and this feature can be used to also test the communication chain from the monitor.

## Conclusions:

- Single use sensors are robust technology to be considered for qualification in a GMP process
- Qualification data may be available or need to be tested(ie, a validation guide from a supplier)
- Any technology would need to be qualified for its specific use with respect to process conditions and length of the process in continuous processing specifically new products with design features tailored toward continuous manufacturing
- Periodic monitor verification can be performed
- Can be read locally & integrated to higher level systems