BioProcess International eBooks

SENSOR TECHNOLOGIES

ESSENTIAL TOOLS FOR BIOPROCESSING 4.0

Maribel Rios

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Offline measurement **is so last year**

There is an increased focus on in-line techniques for bioprocess monitoring primarily driven by the PAT initiative. Biomass is one of the most important components to monitor on-line and in real-time. A critical process parameter that significantly impacts the critical attributes of the process and product.

Aber's track record, supplying biomass sensors for measuring viable cell density on-line and in real-time, from R&D applications through to critical cGMP manufacturing processes has established us as the first choice for many of the world's leading biopharmas. Not only to monitor and control cell concentration but also to manage critical events during cell production.

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Sensor Technologies

Essential Tools for Bioprocessing 4.0

by Maribel Rios

We Meet Your Single Use Process Monitoring Requirements

PendoTECH® In-Line Sensors are made with USP Class VI materials and are manufactured in an ISO 13485 facility. They may be gamma irradiated and are robust enough for extended re-use. There is no calibration required and are available in a variety of sizes. The sensors connect to monitors that can be integrated to a control system or PC.

Pressure *Conductivity* *Temperature* *UV Absorbance* *Turbidity*

PendoTECH Sensors for BioProcess Containers

- Sensor easily installs into a custom port plate receptacle sealed to a flexible bioprocess container
- Features a double o-ring seal and a stop to ensure the sensor is fully inserted
- No calibration required
- Polyethylene port plate with sensor receptacle seals to the film during the manufacturing process of the container
- After manufacture of the container, the sensor is inserted into the port plate receptacle
- Locking collar holds sensor securely in place
- Conductivity port plate features a guard to protect container from electrodes
- Available for pressure and conductivity

NEW!

Measure Pressure & Conductivity in a BioProcess Container

Applications include: mixing monitoring, integrity testing, level/volume measurement, and safety

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Adding Value To Your Process

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Smart Sensors and Data Management

Biomanufacturers need state-of-the-art sensors for use in advanced designs such as closed, automated, and integrated process schemes. Increasingly, companies want sensor devices that are noninvasive, flexible, and highly sensitive and that can be used in single-use and multiuse applications. Some in-line sensors now available can transmit real-time data to a wireless device (e.g., laptop or tablet) through Bluetooth technology. Smart sensors also are gaining prominence for their ability to recalibrate automatically, and they are typically used with a software system. Such smart devices are part of the push toward digital manufacturing and what has been referred to as "Industry 4.0." The Internet of Things (IoT) and the Industrial Internet of Things (IIoT) are novel technical paradigms that allow instruments, complex information systems, and process equipment (all "things") to be connected and communicate through the Internet. IoT sensors connected to smart devices can obtain data from pumps, reactors, laboratory equipment, and other machines and devices. Such sensors also can be connected to IoT networks directly or indirectly. The ideal set-up would be to establish a wireless sensor network (WSN) within an IoT structure.

To gain perspective on modern technologies and design approaches in bioprocess facilities, I spoke with Matt Roesch, senior director of life sciences at JLL Life Sciences.

Reducing Time to Market

Biomanufacturers are seeking ways to reduce time to market. What innovations are likely to help them achieve that goal? Having spent over 30 years in the life sciences industry, I always have approached this question by considering the impact that some technologies have had on both good manufacturing practice (GMP) facilities and non-GMP facilities. Overall, the innovations that have been the most active in the industry are smart sensors, which are leading to uses of predictive analytics.

Many companies and consumers face different options among newer technologies and are seeking applications for them in industrial sectors, including life sciences. A common example is new sensor technology to measure temperature and humidity. It has applications both for GMP and non-GMP settings in modern facilities, but such sensors also can be great for troubleshooting in existing facilities with Wi-Fi capabilities. Extending Wi-Fi capabilities to remote facilities is less expensive than having a centralized building or utility management system. Wi-Fi technology also can retrieve good data for troubleshooting or extending capabilities, and that capability has opened up the playing field for much better data at lower costs.

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For a GMP environment, few of the newest technologies are validated as required. So you need be careful when thinking about using new sensor technology in a GMP area. For example, suppose you want to know temperatures in a cold room or other environment. As soon as you set up a system for that, the data you gather could have a GMP quality impact. So you need to think about what you're going to do with those data, especially if you obtain a reading that falls outside of your validated parameters.

Many environmental temperature sensors can gather real-time data. I have had some experience with sensors that generate discrete data about every 10 minutes, but the newest sensors now are gathering data every five seconds. Some pH sensors take readings over short periods, but those data may or may not be meaningful, depending in part on whether you are obtaining batch results or real-time results.

Data Evaluation in GMP and Non-GMP Environments

How can the data generated by new sensors change how operators do their jobs? Once you start gathering data, and you're validated for certain parameters of pH, for example, you need to decide what to do if the data point falls outside of those parameters. Is that result a problem? Do you have to raise an incident and then investigate a deviation? Do you have to have product put on hold? You need to go back to look at the science to determine what that supports. Innocent acts in a facility can lead to significant outcomes if you aren't thoughtful up front from a GMP standpoint.

In terms of facility design, compare the GMP space of your pilot plant and manufacturing space with your office and even your research and development spaces, for example. The environmental needs are different for all of those spaces, and the division is a fundamental distinction. I've seen some people innocently get themselves in a potential trap by not taking those factors of GMP and non-GMP spaces into consideration.

Any time you gather data in a validated space, you're potentially making those data part of the official record. Some new sensors are being used for diagnostics, and some are available at relatively inexpensive costs for use in commercial buildings. But their software and hardware are not validated to Food and Drug Administration (FDA) standards. So even though the data are real, they are not being gathered through validated sources.

You can get into difficult situations when you gather data in validated and nonvalidated spaces without factoring in the state of those areas. For example, when you're conducting a test outside of a validated state, and the data gathered will be used solely for making adjustments, then you could perform a validation separately. That might be okay. In such a scenario, it comes down to the quality perspective of each organization. But when you're doing that same task in a validated area, then you have to be aware that the data being taken from sensors could be used for records. Just because we

Any time you gather data in a validated space, you're potentially making those data part of the **OFFICIAL RECORD.**

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can gather data inexpensively and collect more than we ever have before doesn't mean that we should.

Some of us who have been in the industry a long time have had to face these questions: What are we going to do with all the data gathered? What kinds of decisions are we going to make? You can experience data overload with the capabilities of new sensor technologies available right now. Many engineers can get themselves in the same trap of wanting more and more data for different parameters, whether those data are meaningful or not.

Some central systems can be set up to gather information. But then when you augment that with a lot of IoT technology, then you need to determine how to analyze and filter those data, which is the case for many large and even medium-sized companies. They often invest significant money with major manufacturers of utility or building management systems. Those systems depend on particular applications, which may or may not be validated. If a system is validated, then some biomanufacturers want to have everything tied into that system. If those applications are not validated, then companies have data historians for analytics. Even for general facility parameters, you need to determine how to integrate new technologies into your existing technology platforms, hardware, software, data, and data-storage systems.

Understandably, biomanufacturing companies are reluctant to seek out different technologies unless there is a specific application that their current platforms do not meet. If you're trying to bring in additional new technology, how do you integrate that into your existing technology platforms? One solution that my company has seen with some clients is using predictive analytics and vibration data.

With traditional vibration data from sensors, data points can be a fairly extensive part of a mainframe central system. By contrast, some startups and newer companies gather data at a fraction of the cost and at capacities not available with a mainframe large system. Generally, if you're gathering that type of data, you are doing so to support valuable pieces of equipment.

Those data also may be critical to sustaining environmental operations such as maintenance, although such operations are not likely to be in critical GMP spaces. We've seen some traction in this area from clients who are feeling that there's real value and insight in gathering data from such operations because doing so provides real information about their operations.

About the Author

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Single-Use Sensors for Bioprocess Monitoring

Single-use sensors have been widely adopted for use in disposable bioreactors and other unit operations from purification chromatography to final fill–finish. PendoTECH develops sensors for real-time measurement and process control for parameters such as pressure, temperature, conductivity, absorbance, and turbidity. BPI spoke with Dennis Annarelli, PhD (Vice President, Operations), about the validation, sterilization, and applications of single-use sensors as well as his thoughts about the future of these devices.

Performance and Applications

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Under what process conditions are single-use sensors a good option? Single-use sensors are cost-effective and robust devices that can be used for most, if not all, typical biopharmaceutical development and manufacturing processes. They have been qualified for use in continuous manufacturing and are gamma compatible.

How are single-use sensors validated, and how are users ensured of accuracy? Because single-use sensors typically cannot be calibrated after they are installed in tubing and bags, maintaining tight manufacturing tolerances and/or precalibration before use must be carried out flawlessly, regardless of manufacturing scale. All sensors must be tested against NIST standard. They are 100% tested before release with this backed-up by a certificate of quality.

How is sterility ensured? Single-use sensors are not available presterilized. Validaton has been carried out to support gamma irradiation after installation in single-use assemblies. More that one gamma exposure to most materials can damage some sensors immediately or lead to increased deterioration. Manufacturing is performed in Class 7 cleanrooms to minimize bioburden.

How are leachables and extractables minimized? Using well-characterized materials for product contact (e.g., polycarbonate and

Figure 1: PendoTECH's new port plate sensors for conductivity (LEFT) and pressure (MIDDLE, RIGHT)

polysulfone) from long-established suppliers ensures that extractables and leachables are minimized. PendoTECH also has carried out a controlled extractables study of its single-use sensors, results of which are available on request.

What performance characteristics must single-use sensors possess? As with any sensing and measurement technologies, accuracy and precision of single-use sensors are a priority. Robustness is important. For example, devices should be unaffected by gamma irradiation and continuous use for extended times.

A Bright Future

What challenges have you faced in mass producing single-use sensors for good manufacturing practice (GMP) processes? Because single-use sensors typically cannot be calibrated after they are installed in tubing and bags, maintaining tight manufacturing tolerances and/or precalibration before use must be carried out flawlessly regardless of manufacturing scale. Having adequate cleanroom space for sensor manufacturing is critical because single-use sensors are made in ISO class 7 cleanrooms. Supply chain control requires significant attention because assurance of supply of critical components must be maintained as volume increases.

How has your sensor business expanded with the growing implementation of single-use manufacturing? We've expanded both manufacturing capacity and sensor process connections. And we are continually exploring new and different sensing technologies such as mesuring pressure and conductivity through a port plate installed on a bioprocess container.

Where do you see the future of single-use sensors heading, and what is PendoTECH doing to anticipate future needs? The future is very bright for single-use sensors as more biopharmaceutical manufacturing moves to complete single-use systems. Cell and gene therapy, because of its scale, naturally works for single-use systems and sensors. PendoTECH is preparing for continued growth by expanding ahead of demand, ensuring that a wide range of process connections are available for all its sensors, and adding new sensing technologies to meet the evolving needs of our customers. Additionally, expanding the hardware options such as digital communication with different protocols to read the sensors is critical as more sophisticated integration of sensors evolves.

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Dennis Annarelli

Single-Use Sensors for Batch and Continuous Bioprocesses

At the BioProcess International Theater at The 2019 BIO conference, Jim Furey (CEO, PendoTECH) spoke about the qualification of single-use sensors for batch and continuous bioprocesses. He emphasized that single-use sensors are durable and can help biomanufacturers minimize their cost of goods. Because continuous processes tend to run longer than batch processes, he suggested that biomanufacturers consider the time and type of sensor exposure as well as the susceptibility of each model to drift or change in calibration over time. He provided results of studies proving the durability, stability, and high performance of PendoTECH's pressure, conductivity, absorbance, and temperature sensors over time. These devices are manufactured to tight tolerances. The company also has developed 1/8-inch size sensors for tubing typically used in continuous bioprocessing and with storage containers (continuous measurements). PendoTECH also has eliminated the need for calibration for each of its sensor technologies. Finally, he reviewed the role of sensors in Industry 4.0 devices and advanced communication systems. Watch the complete presentation at http://video.bioprocessintl.com/bpi-bio-theater-2019-pendtech.