Application Note

PENDOTECH
Leading Process Analytics

Integrated Sensor Solutions

for Scalable Continuous Bioprocessing

Continuous bioprocessing offers significant advantages in terms of process efficiency, scalability, and resource utilization. However, ensuring consistent product quality throughout continuous operations and adhering to stringent regulatory compliance are critical challenges that must be addressed. Maintaining high-quality manufacturing standards and meeting regulatory requirements are essential to guarantee the safety, efficacy, and reliability of biopharmaceutical products produced via this method.

Background

Continuous bioprocessing is a manufacturing approach in which raw materials are continuously fed into bioreactors, and the product is harvested in a steady, continuous flow. This method must maintains an optimal environment for cell or microorganism growth by controlling key parameters such as temperature, pH, nutrient supply, and waste removal. Although the concept has existed for decades, recent technological advances and growing demand for biopharmaceuticals have accelerated its adoption. Continuous bioprocessing emphasizes closed systems to minimize contamination risks, especially during prolonged downstream processing, with synchronized unit operations managed by centralized control systems.[1]

These controls reduce variability, improve product quality, and lower human intervention, enhancing efficiency and reducing costs. However, challenges remain, including system complexity, evolving regulatory frameworks, scalability issues, and the need for specialized operator training.

METTLER TOLEDO

Process

Continuous bioprocessing involves linking two or more unit operations through fluid flow, which can be achieved in three primary ways: direct connection where flow rate and stream composition are compatible with the next unit (e.g., normal flow filtration); direct connection with in-line conditioning where flow rates are compatible but the feed stream requires adjustment such as pH or conductivity; and indirect connection via a surge vessel, which decouples unit operations when flow rates are incompatible, helping to control minor process upsets. This integrated approach offers several benefits, including increased efficiency by maintaining continuous material flow, which reduces downtime and boosts productivity. It also enables tighter control of process parameters, reducing variability and enhancing product quality through real-time monitoring, and helps adjust for deviations.[2]

Additionally, continuous bioprocessing can lower costs by minimizing waste, reducing energy consumption, and optimizing resource use. However, challenges such as system complexity and regulatory hurdles remain, necessitating strategies to overcome these obstacles for successful implementation.

Challenges

Despite its numerous benefits, continuous bioprocessing presents several challenges that must be addressed for successful implementation. The complexity of continuous systems demands advanced process control and monitoring technologies to maintain stability and product quality. Additionally, regulatory frameworks for continuous bioprocessing are still evolving, creating hurdles for compliance and approval.

Scalability poses another challenge, as designing and implementing systems that can efficiently scale from development to commercial production requires careful planning. Finally, the specialized training and expertise needed for operators and maintenance personnel add to the operational challenges, emphasizing the need for comprehensive training programs and skilled workforce development.

METTLER TOLEDO Solutions

Implementing advanced sensors for pressure, conductivity, pH, temperature, and UV absorbance provides robust process control and real-time monitoring, helping maintain stability and product quality. These sensor technologies support regulatory compliance, facilitate scalable designs, and reduce operational risks, making them essential tools for successful continuous bioprocessing implementation.

Pressure Sensor

METTLER TOLEDO Pendotech's Single-Use Pressure Sensors provide accurate measurement of both static and dynamic pressures in gases and liquids within biopharmaceutical applications. Designed for disposable use, these sensors offer a dependable alternative to traditional stainless steel pressure transducers. Featuring High Accuracy Pressure (MEMS-HAP) chips, they are well-suited for monitoring processes such as bioreactor, filtration, chromatography, ultrafiltration/diafiltration, and final formulation.

These devices operate across a pressure range of -11.5 to 75 psi (-0.79 to 5.2 bar). Their design ensures a clear flow path without dead legs, minimizing hold-up volume compared to conventional stainless-steel transducers or gauges. Accuracy varies with pressure levels: ±2% for 0–6 psi, ±3% for 6–30 psi, and ±5% for 30–60 psi. These sensors integrate seamlessly with transmitters such as PressureMAT™ and the Pendotech Process Control System, delivering reliable, high-precision data up to 75 psi. The sensors support various connection types, including hose-barb fittings ranging from 1/8 to 1.5 inch (3.175 mm -– 25.4 38.1 mm), sanitary flanges, and luer connectors.

Constructed from polycarbonate or caustic-resistant polysulfone, all fluid-contact materials meet USP Class VI standards before and after irradiation. Each sensor batch includes a Certificate of Conformance, with individual NIST Certificates available upon request. Manufactured in an ISO 9001-certified facility with an ISO Class 7 clean room, these sensors are compatible with gamma and X-ray irradiation and feature a test port for non-invasive in-place testing.

Conductivity Sensor:
METTLER TOLEDO Pendotech Single-Use Conductivity Sensor and Conductivity Monitor offer a precise, calibration-free solution for measuring conductivity and temperature in various unit operations during the entire bioprocess. Featuring automatic temperature compensation to normalize readings to 25°C, these sensors measure conductivity from 0.1 to 100 mS/cm and temperatures from 2°C to 50°C. They support pressures up to 75 psi (5 bar), are made from gamma-compatible fluid path materials, and include integrated temperature measurement for reliable data.

The conductivity monitor provides 4-20 mA outputs for both conductivity and temperature, enabling seamless integration with control systems such as PLCs or DCS, as well as an RS-232 output for PC data collection. Available with various polysulfone hose barb sizes, these sensors ensure complete buffer exchange, enhancing process efficiency and product quality through high-accuracy conductivity measurement across different levels.

pH Sensor:
The single-use pH sensor from
METTLER TOLEDO Penodotech integrates advanced InSUS™ 307 pH probe technology with a single-use flow cell optimized for in-line sensing in downstream bioprocessing. It includes a pH-sensitive electrode, reference electrode, and temperature probe to accurately measure hydrogen ion concentration via potential difference. Available in two pre-assembled sizes and compatible with gamma irradiation sterilization, this sensor requires no calibration, minimizing process downtime and integrating seamlessly with METTLER TOLEDO transmitters for reliable pH monitoring. Pendotech Single-Use In-Line pH Sensors are available in polysulfone with 3/4- inch sanitary flange or 1/4-inch hose barb fittings, offering options with either a 1-year or 2-year shelf life.

The METTLER TOLEDO Pendotech pH Probe is engineered for precision and reliability across various process development applications, allowing easy probe replacement to prevent cross-contamination. The flow cell is offered in two sizes—a 1/4-inch hose barb and a 3/4-inch sanitary flange—designed for in-line measurements that effectively prevent flow interference and back pressure. This combination of a probe and a flow cell ensures efficient, accurate pH measurement in bioprocessing workflows.

Temperature Sensor:
METTLER TOLEDO Pendotech Single-Use Temperature Sensors offer precise, reliable temperature measurement for single-use bioprocess applications, preventing cross-contamination while being durable for multiple cleanings. Designed for in-line use in filtration, chromatography, TFF, filling, and general monitoring, they feature high accuracy (better than ±0.2°C) across 0-70°C without needing calibration. Made from polysulfone, they comply with USP Class VI and are produced in FDA-registered, ISO 9001-certified facilities.

Compatible with various monitors, including TEMP-340 and PDKT-TT, they provide reusable cables and connectors designed to prevent misconnection. Available with hose-barb, sanitary flange, or luer fittings, they ensure unobstructed fluid paths and seamless integration with control systems, offering a cost-effective, and versatile solution for precise temperature control in bioprocessing.

Application Note

UV Absorbance and Turbidity Measurement:
The METTLER TOLEDO Pendotech PM2 photometer is a versatile instrument designed for both laboratory and process environments, available in benchtop and panel mount versions. It offers pre-configured options with seven wavelength combinations and supports multiple data acquisition systems through two 4-20mA outputs and digital communication protocols. The device provides real-time, non-invasive UV absorbance measurements to accurately detect target molecules, concentration changes, and absorbance peaks. It features gamma-irradiatable flow cells paired with a compact PM2 photometer and fiber optic cable for seamless integration into chromatography processes without product sampling. Various flow cell sizes and path lengths accommodate diverse applications and process scales.

The Pendotech PM2 Photometer is also available in a dual-wavelength version with two LED light sources selectable among 260 nm, 280 nm, 300 nm, or 880 nm, enabling simultaneous measurement at two wavelengths. This enhances biopharmaceutical monitoring by supporting turbidity measurements at 880 nm to assess filter performance directly from bioreactors or fermentors, helping detect filter breakthrough and loss of capacity.

Conclusion
Continuous bioprocessing represents a transformative approach in biomanufacturing, offering enhanced efficiency, scalability, and resource utilization compared to traditional batch processes. However, the complexity of maintaining consistent product quality and meeting stringent regulatory requirements presents significant challenges. This necessitates integrating advanced sensor technologies—such as for pressure, temperature, pH, conductivity, and UV absorbance—that enable precise, real-time monitoring and tight process control. These sensors not only reduce variability and ensure stable operation throughout scale-up but also support regulatory compliance through detailed data capture via transmitters.

METTLER TOLEDO's comprehensive sensor solutions provide the reliability, scalability, and integration needed to navigate the complexities of continuous bioprocessing, ultimately facilitating the production of safe, effective, and high-quality biopharmaceuticals from development to commercial scale.

References
1. Continuous downstream processing for biomanufacturing: an industry review, BioPhorum, June 2019
2. Developing & Implementing A Continuous Bioprocess Control Strategy, BioPhorum, 2024

Mettler-Toledo Pendotech
Process Analytics

www.pendotech.com
For more information

PA4183en A
MarCom Plainsboro, USA