

Precision in Every Solution

Advanced Sensors for Bioprocessing

Bioprocessing harnesses living cells to produce pharmaceuticals, biofuels, and other valuable products through complex upstream and downstream stages. Scaling operations from laboratory to industrial scale requires precise control of biological and fluid parameters, often managed via advanced sensor technologies. Single-use sensors have become integral in maintaining sterility, reducing contamination, and enhancing process adaptability. Monitoring critical variables such as pH, dissolved oxygen, temperature, conductivity, pressure, and UV absorbance in real-time supports optimal growth conditions and product quality.



Background

Bioprocessing utilizes living cells and their components—such as bacteria, yeast, mammalian cells, microbes, plants, animals, and fungi—to produce valuable products including pharmaceuticals, vaccines, biofuels, food ingredients, and chemicals. The process occurs in stages, beginning with upstream processing where cells are cultivated in bioreactors (fermenters) under controlled conditions to optimize growth and biochemical reactions. After this, downstream processing involves isolating, purifying, and recovering the desired product, depending on whether it is located inside the cells, outside the cells, or in whole-cell form. These coordinated steps convert biological materials into essential products that impact various industries.

Bioprocessing Scale-Up and Integrated Single-Use Sensor Technologies

Scaling up bioprocessing from lab-scale to large industrial bioreactors involves managing complex biological components like biomass, gases, and liquids, while precisely monitoring critical fluid properties (viscosity, density, and concentration) along with parameters like UV light, conductivity, pH, temperature, air, and pressure. The final purification stage is often the most challenging, requiring rigorous sterilization—typically using stainless steel equipment cleaned by heat or chemicals—and purification methods including filtration, chromatography, and precipitation.

An increasing array of analytical and physical parameters are now monitored in real-time and inline through the use of single-use sensors integrated throughout the bioprocessing workflow. These sensors, designed for disposal or compatibility with single-use systems, can be effortlessly embedded into bioreactors, filtration units, chromatography processes, and formulation equipment, maintaining sterility and reducing contamination risks. By continuously tracking and managing critical growth conditions during upstream bioprocessing and ensuring quality control in downstream purification, these sensors—when combined with data management systems—support process optimization and help meet regulatory requirements across manufacturing. The complete bioprocessing workflow—from raw material preparation to final filling and packaging—requires continuous monitoring and control to maintain process integrity. Key steps include preparing large-volume buffers essential for cell growth, such as those used in ultrafiltration-diafiltration and final formulation, overseeing cell cultivation within bioreactors, and performing cell harvesting. Consistent regulation of these stages ensures product quality and process reliability throughout manufacturing.

Key Process Parameters (KPPs) play a crucial role throughout each stage of bioprocessing to ensure optimal performance, product quality, and process efficiency. Here is an overview of how **KPPs are regulated and monitored across the main bioprocessing steps:**

1. Cell Harvesting:

- KPPs include cell viability, biomass concentration, temperature, pH, and flow rates.
- These parameters are monitored to maximize cell recovery and minimize damage during removal of cells or debris, typically by centrifugation or filtration.

2. Primary Recovery:

- Critical parameters include solids concentration, turbidity, pressure, and flow rate.
- Maintaining optimal conditions ensures effective separation of product from solids using techniques like centrifugation or depth filtration.

3. Purification:

- Parameters such as buffer composition, pH, conductivity, temperature, and flow rates are tightly controlled.
- Chromatography methods (affinity, ion exchange, size exclusion) rely on these parameters to selectively isolate the target biomolecule.

4. Concentration:

- Ultrafiltration parameters like transmembrane pressure, flow rate, temperature, and concentration factor are regulated.
- Proper control prevents fouling and ensures efficient product concentration.

5. Formulation:

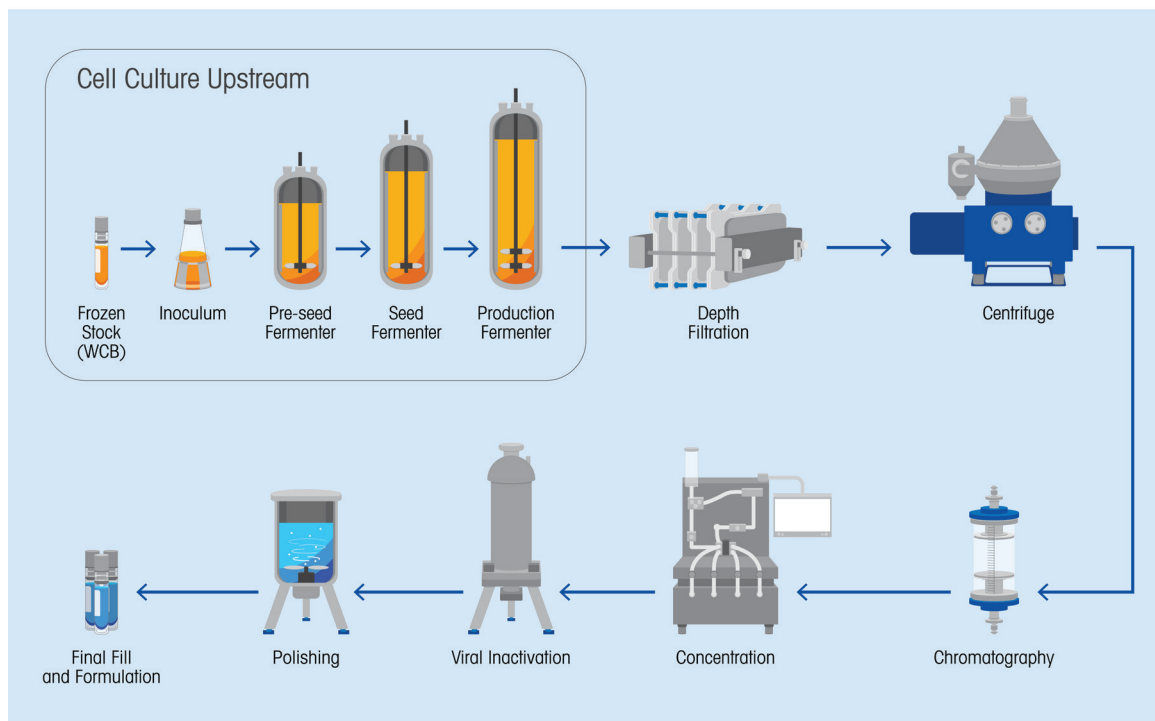
- Parameters include product concentration, pH, stabilizer levels, temperature, and mixing rates.
- These factors are monitored to achieve the desired final product form (liquid or lyophilized) and stability.

6. Sterile Filtration:

- Key parameters involve filtration pressure, flow rate, integrity testing, and sterility assurance.
- Continuous monitoring guarantees removal of contaminants and maintains product sterility.

Throughout all stages, real-time monitoring and control systems—often integrating single-use sensors and advanced data analytics—help regulate these KPPs. This integration enables rapid detection of deviations, process optimization, and compliance with regulatory standards, ultimately ensuring high-quality, consistent bioprocessing outcomes.

Downstream Processing



Challenges in Bioprocess Parameter Monitoring

pH: In bioprocessing, it is often necessary to maintain pH within a narrow range to achieve optimal productivity. However, pH fluctuations frequently occur due to various factors. To prevent deviations beyond the ideal range, an effective pH control system is essential. This system relies on precise pH sensors connected to a control loop that can accurately administer calculated amounts of acid or base to adjust the pH as needed. In upstream bioprocessing, maintaining pH is crucial for optimal cell growth and productivity, while in downstream processing, controlling pH is vital to preserve product stability and quality during purification steps, utilizing accurate sensors and dosing of acid or base to maintain the desired pH.

Dissolved Oxygen (DO): Many microorganisms depend on oxygen for essential cellular functions such as respiration. However, oxygen requirements can vary not only between different species but also among strains. Oxygen is vital in upstream bioprocessing for microbial respiration, affecting growth and product synthesis, making its monitoring essential. In downstream processing, maintaining proper oxygen

levels is important to prevent product oxidation and ensure stability.

Temperature: Temperature control is essential throughout bioprocessing. In downstream steps such as purification and filtration, controlling temperature preserves protein stability, enhances purification efficiency by maintaining proper binding and flow characteristics. It also ensures final product shelf life and formulation integrity by preventing degradation.

Conductivity: Maintaining conductivity in both upstream and downstream bioprocessing is vital for ensuring smooth and efficient operations. In upstream processing, conductivity helps monitor nutrient levels, control feed strategies, detect contamination, and optimize cell growth by reflecting the ionic strength of the culture media. In downstream processing, it is crucial for buffer preparation, chromatography performance, in-line dilution accuracy, and process monitoring to maintain product quality and consistency. Overall, stable conductivity supports product quality, process efficiency, and regulatory compliance by serving as a critical process parameter in biopharmaceutical production.

Pressure: In upstream bioprocessing, oxygen is critical for microorganisms' cellular functions like respiration, with requirements varying among species and strains; insufficient dissolved oxygen can reduce metabolic rates, alter growth, change product synthesis, or cause cell death, making its monitoring and regulation essential for optimal cell cultivation. In downstream processing, while oxygen demand is typically lower, maintaining appropriate oxygen levels during steps such as purification can be important. This helps prevent oxidative damage to the product, ensures its stability, and supports overall bioprocess success.

UV Absorbance: In upstream processing, UV absorbance aids in cell growth monitoring by estimating biomass concentration through optical density at 600 nm. This helps detect contamination by observing deviations in absorbance profiles. During downstream processing, UV absorbance quantifies purified proteins, assesses purity through absorbance ratios (like A260/A280), and supports real-time process control decisions. Advanced variable path length UV absorbance techniques enhance accuracy by eliminating dilution errors. This real-time, in-line monitoring reduces off-line analyses and process interruptions, enhancing efficiency.

Navigating the Challenges of Bioprocess Parameter Monitoring

pH Sensors: METTLER TOLEDO pH sensors are engineered to fulfil diverse pH control needs accurately. Its in-line pH analyzers provide precise measurements in various settings, from ultrapure water and hygienic bioreactors to demanding chemical production environments. Featuring digital Intelligent Sensor Management (ISM™) technology, these sensors offer predictive diagnostics to reduce maintenance. The single-use InSUS™ 310 sensor, designed for direct integration into single-use bioreactor bags, delivers reliable pH signals for at least six weeks, making it ideal for long batch processes. In downstream processing, real-time pH measurement is vital due to dynamic liquid flow and rapid pH shifts. Electrochemical pH sensors offer the required accuracy and fast response. A flow cell securely holds the probe within the tubing, meets

pressure requirements, and eliminates the need for process calibration. It provides a pre-calibrated, single-use in-line pH sensor that is gamma irradiation compatible, fully biocompatible for GMP use with material traceability, suitable for process development, and compatible with existing METTLER TOLEDO transmitters.



Dissolved Oxygen Sensors: The single-use dissolved oxygen (DO) sensor utilizes optical spot (fluorescence quenching) technology to provide fast, accurate, and stable DO measurements, ideal for extended cell culture processes. It features a short pre-conditioning phase for rapid start-up and ensures easy, secure installation in single-use bag ports. Manufactured from USP88 Class VI-compliant materials, it is compatible with gamma and X-ray sterilization, guaranteeing biocompatibility and process safety. The InSUS 607 sensor is specifically designed for integration into single-use bags and delivers reliable performance throughout biopharmaceutical manufacturing. Furthermore, its reusable sensor head, the InSUS H60i, is compatible with METTLER TOLEDO field transmitters and various third-party biocontrollers, allowing for flexible integration.

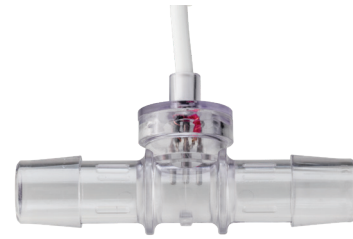


Temperature Sensors: METTLER TOLEDO

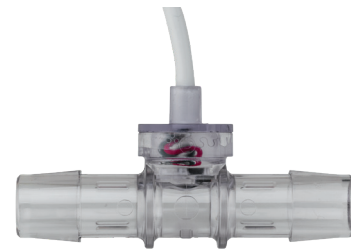
Pendotech's temperature sensors offer precise, reliable measurements for filtration, chromatography, and filling processes. Designed for seamless in-line integration, they prevent fluid obstruction and pressure drops. They operate across a broad temperature range and come pre-calibrated for immediate and accurate use. Compatible with monitors like the TEMP-340 handheld unit via reusable cables, they feature hose-barb, sanitary flange, or luer fittings to ensure unobstructed flow. Using a thermistor element, they require no calibration. Cable lengths vary by fitting type, and an alignment guide facilitates quick, secure connections with sensor status indicated on the monitor.



Conductivity Sensors: Single-use conductivity sensors from Pendotech are designed for use in critical bioprocess operations. METTLER TOLEDO Pendotech Single-Use Conductivity Sensors provide accurate conductivity (0.1 to 100 mS/cm) and temperature (2°C to 50°C) measurements without the need for calibration, due to a pre-set cell constant configured in the monitor or transmitter. An optional one-point calibration is available if necessary. The conductivity transmitter connects directly to the sensor and outputs a linear 4-20 mA signal normalized to 25°C across a 0-150 mS range. Featuring a convenient DIN rail mounting design, the transmitter ensures easy installation and reliable performance. Raw conductivity and temperature values are read from the sensor, used to calculate normalized conductivity at 25°C, and transmitted via the 4–20 mA signal.



Pressure Sensors: METTLER TOLEDO Pendotech's Single-Use Pressure Sensors offer accurate and cost-effective measurement of both static and dynamic pressure for gases and liquids in biopharmaceutical processes. Featuring High Accuracy Pressure (MEMS-HAP) Chips, these sensors are ideal for applications such as filtration, chromatography, monitoring of gas and disposable bioreactors, filling operations, and more. Made from caustic-resistant polysulfone, they withstand sanitization procedures. Rated for use up to 75 psi, these sensors are compatible with the PressureMAT™ monitor/transmitter, Process Control Systems, and approved third-party monitors. Rely on these pressure sensors for consistent, dependable performance in your biopharmaceutical workflows.



UV Absorbance and Turbidity Sensors: METTLER TOLEDO Pendotech provides In-line Single-Use UV Absorbance and Turbidity measuring and monitoring tools that collect data directly from bioprocess fluid streams, minimizing disruption compared to off-line measurements. Its Single-Use UV Flow Cells paired with a compact PM2 Photometer and fiber optic cables measure UV absorbance in filtration and chromatography applications without contacting the product. Turbidity Flow Cells with the PM2 Photometer assess turbidity of unclarified material from bioreactors

or after filtration, ensuring consistent filter performance. The UV and Turbidity transmitters integrate with monitors or control systems for combined data acquisition and control. A dual-wavelength unit and capability for two parallel measurements with one flow cell add versatility. These tools enhance efficiency and reliability in bioprocess monitoring.



Conclusion

METTLER TOLEDO leads the way in scaling bioprocesses from laboratory to industrial levels by providing advanced sensor technologies that enable meticulous regulation of biological and fluid parameters. Its single-use sensors improve sterility and enhance process flexibility while delivering continuous real-time monitoring of key process parameters such as pH, dissolved oxygen, temperature, conductivity, pressure, and UV absorbance. These precise measurements ensure optimal conditions during both cell cultivation and product purification, supporting consistent product quality. METTLER TOLEDO's innovative sensor solutions facilitate seamless integration, reliable data acquisition, and compliance with regulatory standards throughout the manufacturing process.

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