White paper

Revolutionizing biomanufacturing with real-time, inline bioprocess measurement

How to streamline drug development from lab to process, increase operational insights and efficiency, and achieve high-quality production to maintain a competitive edge

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The biopharmaceutical manufacturing industry is facing ever-increasing demands for rapid development and more efficient production of life-saving medications. This pressure stems from a multitude of factors, including the rise of chronic diseases, a growing global population, and the rising pursuit of personalized medicine.

To keep pace with these needs, manufacturers must adopt innovative technologies and methodologies into their workflows, including digital sensors and Raman measurement in production environments. These efforts will enable accelerated drug development timelines, improve operational efficiency, and enhance product quality.

This white paper explores how integrating inline measurement technologies into both upstream and downstream process control strategies provides a significant competitive advantage in this evolving biopharmaceutical landscape. Whether developing new therapies, scaling production to meet market needs, or optimizing existing processes, understanding and implementing real-time bioprocess monitoring is critical for drug efficacy and operational success.

Conventional measurement challenges

Biopharmaceutical manufacturers face numerous challenges throughout the product lifecycle, starting with the need to minimize new product development timelines. The race to bring novel therapies to market—often amid fierce competition, and always with stringent regulatory requirements—demands rapid development cycles, efficient process optimization, and reliable data for regulatory approval.

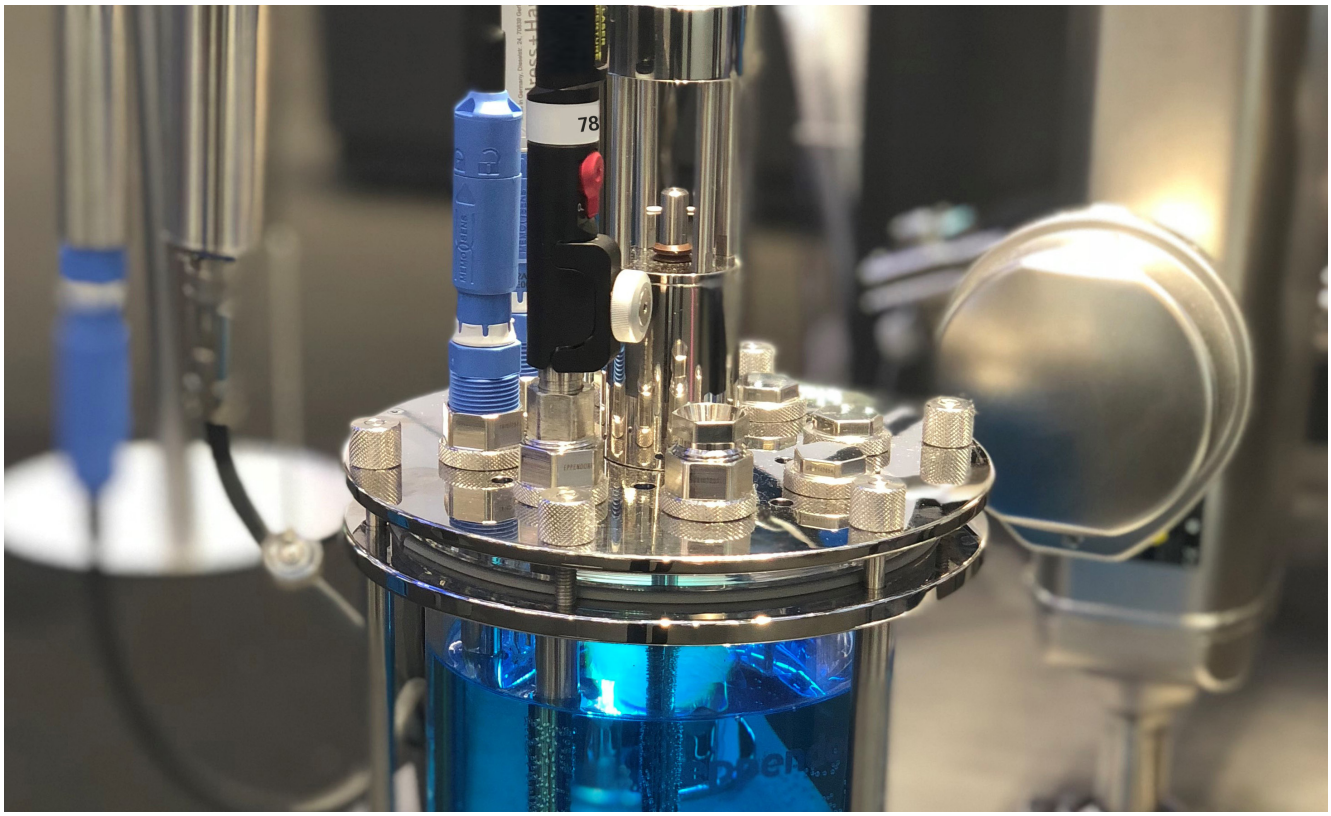
Successfully transitioning a drug from its humble origins in a laboratory to large-scale, commercial production is no small undertaking. The scale-up process must maintain crucial quality checks and balances through every stage of development as procedures are passed from one team to another, oftentimes traversing facility boundaries. Each step presents different product quality and yield challenges, including material changes, varying equipment size, and different operating parameters.

As a biologics manufacturer progresses through the product development lifecycle, traditional methods of sampling and analyzing production parameters offline in a lab can create bottlenecks on the facility floor, delaying critical decisions and extending development timelines. These offline measurements provide neither the reliability nor the agility to ensure required performance at scale, which can lead to cost-intensive trial-and-error adjustments and potential batch failures. Additionally, infrequent sampling for offline analysis often fails to capture the dynamic nature of bioprocesses, limiting opportunities for optimization and increasing the risk of process contamination.

Driving innovation with inline measurement

Inline measurement addresses these and other issues by providing continuous data throughout the scale-up process for near-real-time insights into process and equipment health. This data empowers manufacturers to make informed decisions quickly and optimize processes for improved efficiency and quality, enabling them to identify and address potential issues early, which ensures a smoother transition from development to commercialization.

Continuous process improvement is essential for maximizing efficiency, cost-effectiveness, and product quality. Even small improvements in yield or reductions in waste can have significant impacts on profitability. The data streams provided by inline measurement result in a comprehensive and dynamic understanding of the process, enabling manufacturers to identify bottlenecks, optimize resource utilization, and implement data-driven improvements that enhance both economic and environmental sustainability.



Leading instrument suppliers, like Endress+Hauser, utilize the same measurement technologies in both lab and inline process instruments, ensuring a smooth journey through the drug development lifecycle.

Key trends are converging to revolutionize biopharmaceutical manufacturing and provide additional solutions to aforementioned challenges. Intensified and continuous bioprocessing fueled by process analytical technology (PAT), quality-by-design (QbD), and Pharma 4.0 principles are transforming the industry. Real-time process understanding and control are paramount to ensure consistent product quality throughout continuous operations. These approaches rely heavily on real-time data acquisition and analysis, reducing the need for end-product lab testing, and instilling a greater emphasis on quality assurance through proactive and preventive methodologies.

Increasing adoption of single-use bioreactors

High-throughput development is also providing improved efficiencies for manufacturers, driven by the need to screen vast libraries of molecules and cell lines to identify promising drug candidates during research and development. This has led to the adoption of miniaturized bioreactor systems, ranging from micro-bioreactors to single-use bioreactors (SUBs), which enable parallel experimentation and accelerated screening processes.

However, these miniaturized systems require equally adaptable analytical solutions. Inline measurement technologies, with their small footprints and adaptability to various bioreactor designs, are ideally suited to meet these demands.

Some Raman probes offer an ideal interface to high-throughput development through single-use commercial manufacturing through integration with Biostat STR® from Sartorius as well as Ambr®15 and Ambr 250®

The increasing adoption of SUBs—driven by their flexibility, reduced contamination risks, and faster turnaround times—presents both opportunities and challenges for bioprocess monitoring. Traditional sensors, often designed for permanent installation in stainless steel bioreactors, are not compatible with the disposable nature of SUBs. This has spurred sensor design innovation, leading to the development of sterilizable, single-use sensors that can be seamlessly integrated into SUB systems, providing real-time data without compromising sterility.

In upstream processing, where living cells are cultivated to produce a desired biopharmaceutical product, monitoring parameters such as pH, dissolved oxygen (DO), cell growth, glucose levels, and viable cell density in real time is crucial. These parameters directly influence cell growth, productivity, and product quality throughout the product lifecycle. Inline sensors can provide continuous feedback at each stage of development, enabling precise control over these parameters, which spurs higher cell densities, improved product yields, and reduced batch failures.

Equally as important, downstream processing, which entails the purification and formulation of a desired product from complex cell culture broths, also stands to benefit significantly from inline measurement. Traditional downstream processes often rely on multiple offline analytical techniques, which can cause delays and potential product loss. However, measuring downstream parameters inline —such as pH, conductivity, UV absorbance, aggregation, and concentration—facilitates efficient and timely separation and purification, ensuring optimal product quality and yield. This real-time data enables precise control over purification steps, including chromatography, filtration, and buffer exchange, minimizing product loss and maximizing process efficiency.

Raman spectroscopic advantages

Among modern measurement technologies available to biomanufacturers, Raman spectroscopy provides some of the clearest benefits. Unlike many traditional analytical techniques that require sample preparation or separation, non-destructive Raman measurement is conducted in the process, providing chemical composition and concentration analysis directly within a bioreactor. This eliminates the need for time-consuming offline analysis by providing timely data for near-real-time process insights.

Raman spectroscopy is particularly well suited for monitoring critical process parameters, such as glucose consumption, lactate production, and cell culture media analysis. By tracking these and other parameters, manufacturers can optimize cell culture feeding strategies, prevent the buildup of inhibitory byproducts, and maintain optimal nutrient levels—all of which contribute to improved cell growth and product yield.

Beyond process monitoring, Raman spectroscopy plays a key role in ensuring product quality by identifying and quantifying product-related critical quality attributes (CQAs). Even minor structural changes can degrade product safety and efficacy, making timely detection and remediation paramount. Raman measurement's ability to provide detailed chemical composition and structural information makes it an ideal tool for identifying and quantifying CQAs, ensuring final products meet the highest quality standards.

Furthermore, Raman spectroscopy facilitates deep process understanding by providing insights into reaction kinetics and process dynamics. By analyzing patterns in spectral data, scientists gain valuable information about reaction rates, intermediate formations, and overall bioprocess progression. This depth of comprehension enables sophisticated process control strategies, resulting in improved efficiency and product quality.

Digital sensor technology benefits

While Raman spectroscopy is ideal for providing chemical information, digital sensor technology like Memosens complements it by providing continous critical process parameter data.

These sensors, often based on electrochemical or optical principles, provide real-time measurements of parameters such as pH, DO, and conductivity. In upstream processing, these sensors reveal essential information about the cell culture environment, ensuring optimal conditions for cell growth and productivity. In downstream processing, they monitor the efficiency of purification steps and ensure the final product formulation meets the required specifications.

Digital sensors provide unparalleled measurement accuracy and minimal maintenance requirements with reliable non-contact signal transmission technology. Upstream and downstream process parameters are easily captured.

The continuous data streams from these sensors, combined with the chemical information provided by Raman spectroscopy, create a comprehensive and dynamic understanding of a bioprocess. This wealth of data facilitates early deviation detection from desired operating conditions, enabling timely intervention to prevent costly batch failures and maintain consistent product quality. Additionally, the data generated by these sensors can be integrated into advanced process control systems, enabling automated adjustments to process parameters in real time, which further optimizes efficiency, while reducing reliance on manual intervention.

Choosing the right instrumentation and the right partner

Inline measurement technologies in biopharmaceutical environments are also streamlining drug scale up, propelled by consistent measurement methods throughout each stage of product development. By utilizing the same analytical techniques from the lab to the production floor, manufacturers can minimize the risk of discrepancies between lifecycle phases and ensure a smooth transition from research and development to commercialization.

These intrinsic measurement consistencies simplify the technology transfer process, reducing the need for extensive revalidation and requalification efforts at numerous stages. Additionally, the data generated by inline measurement technologies can be used to develop sophisticated process models, which can be used to simulate different operating scenarios and identify further opportunities for optimization.

Choosing the right instrumentation is key for realizing these and other benefits, and for success in today's competitive bioprocessing landscape. When evaluating potential partners, biopharmaceutical researchers and manufacturers should consider a supplier's:

- **Installed base:** is there a far-reaching user base of the instrumentation under investigation, with documented success stories?
- **Portfolio breadth and depth:** does the supplier offer a wide range of sensors and systems covering both upstream and downstream processes, with native inter-compatibility?
- **Scalability and versatility:** can the instruments be easily adapted to multiple bioreactor setups and scales, from small-scale laboratory systems to large-scale manufacturing facilities?
- **Support network:** does the supplier provide a robust global support network, with access to technical expertise, application support, and maintenance services throughout the product lifecycle?

A reliable instrumentation partner provides not only the necessary hardware and software, but it also works closely with end users to ensure successful implementation, integration, and ongoing support.

Implement inline monitoring to streamline product lifecycles

The ability to monitor and adjust process parameters in real-time fosters faster creation of optimal bioprocessing conditions, leading to shorter drug development cycles and quicker time to market. By embracing inline instrumentation technologies, manufacturers can accelerate development, optimize operations, ensure product quality, and deliver life-saving therapies to patients faster and more efficiently.

As biopharmaceutical development and manufacturing continues its fast-paced evolution, real-time monitoring will play an increasingly critical role in shaping the industry's future, leading to safer, more effective, and more accessible therapies for patients worldwide. This increased access to inline and real-time data is driving process optimization, increasing insights, and helping manufacturers maintain regulatory compliance.

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WP01220C/66/EN/01.24

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