Improving Process Stability by Implementing Data Monitoring and Quality Strategies

With product quality and efficient yield being key components of bioprocessing, there are a number of concepts that can be utilised to ensure both aspects are consistently met

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Ensuring consistently high product quality and process stability are key challenges in biopharmaceutical development and production. Real-time data monitoring enables process quality validation and fast decision-making throughout all process steps. Hence, continuous data monitoring and analysis can significantly contribute to managing costs, time-to-market, and quality in bioprocessing.

Biopharmaceutical manufacturing from research lab and benchtop to large-scale production is very expensive and time-consuming. For this reason, concepts have been developed to improve process understanding, and to achieve the previously defined ambitious goals at each step in bioprocessing. Process data and data analysis are the basis to gaining valuable process knowledge, to manage and to control lab work, as well as to transfer small-scale to large-scale production.

PAT to Facilitate the Development and Production of Innovative Products

In order to achieve maximum yield at consistently high product quality, the concept of process analytical technology (PAT) plays an important role in reaching the goal. The PAT concept is intended to enhance the safety and quality of manufactured biopharmaceutical products. PAT helps to understand processes, since it considers the impact of certain parameters on the process performance. It must be integrated into the entire production development, starting with the early stages of process development, and continuing through process scale-up. A well-designed PAT-based process is stable, and ensures that predefined limits for critical parameters and indicators are met, providing high product quality and process reliability. Furthermore, it enables fast and data-driven decision-making. As a result, process stability and robustness can be improved, and process costs and cycle times can be reduced.

With the introduction of PAT, companies are encouraged to continuously monitor and validate process data in real-time. Thus, it is essential to determine critical process parameters (CPPs), which are key variables in the production process that might have an impact on the desired product quality. In general, temperature, pH, and dissolved oxygen are considered as standard CPPs. Other specific CPPs and their impact on product yield are

Flow measurement in process development for data analysis – Source: SONOTEC GmbH

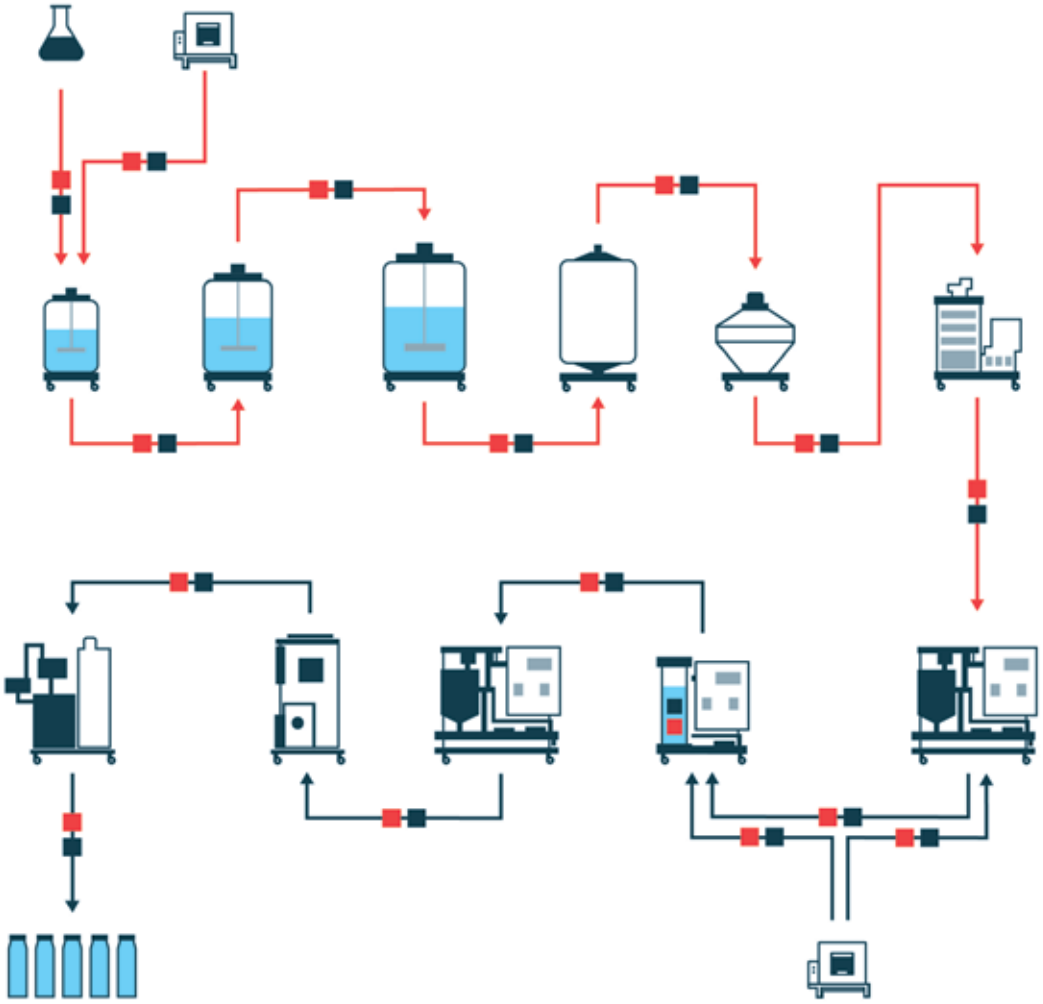
often identified with experiments or statistical approaches. Additionally, CPPs that should not be underestimated are flow rate and flow volume, since both can substantially affect the media concentration – for example, in fed-batch processes.

Even minor deviations in CPPs can have significant effects on critical quality attributes (CQA). CQAs describe physical, chemical, or biological properties or characteristics that should be within a defined limit, range, or distribution to ensure the desired product quality. By implementing sophisticated sensor technology, CPPs can be tracked and controlled to make sure that the entire process complies with the desired quality requirements. In order to monitor flow rates, volume, or to detect air bubbles, non-contact sensors using ultrasonic technology are the preferred choice. As the media does not make contact with the sensors, risk of contamination is reduced. Clamp-on ultrasonic sensors also have no impeller or moving parts in the flow path, and therefore do not cause shear stress on cells. Thus, the product quality is not affected by the measuring device. Another positive side effect of non-contact sensors is that expensive and time-consuming cleaning of the sensors is not necessary, making them cost-efficient and sustainable.

QbD to Achieve Consistent High Product Quality

The introduction of a quality by design (QbD) strategy in pharma is also closely connected with the PAT concept, ensuring process flexibility within the defined framework conditions. The process control defined in a QbD strategy effectively uses process analysis technology to understand processes, and to monitor and track process trends using a number of measurement devices and software tools. In doing so, it ensures that quality attributes are reached and maintained. Consistent real-time data analysis is the key to this approach.

The tracking of CPPs at all relevant process steps can also be considered as preventive and proactive risk management, which is one of the objectives in a QbD development and manufacturing strategy. In summary, the installation of sensors, which continuously monitor and analyse CPPs, save time and money in both R&D and production. Additionally, the development of reliable, reproducible processes, in which deviations are proactively managed, lead to continuous process improvement. Discrepancies or any drift in the CPPs can be detected at an early stage to avoid variations in the product quality, to reduce batch failures, or to prevent any process downtime.



Example for continuous flow measurement and air bubble detection starting in upstream and finishing with filling in downstream, Source: SONOTEC GmbH

GMP-Compliant Sensor Technology to Monitor Process Data in Real-Time

The primary goal in biopharmaceutical production is consistently high product quality, which is achieved by high process stability and continuous data monitoring. Thus, for measuring CPPs, the implemented sensor technology should not have any negative impact on the upstream and downstream processes. Small and compact ultrasonic sensors with integrated electronics can easily be added and installed in established or newly developed processes. In this way, processes are upgraded and made more secure without complex system modifications.

The clamp-on design of ultrasonic flow meters and air bubble detectors is ideally suited for single-use bioprocessing tubing. It ensures reliable measurement of flow rates or volume, as well as fail-safe air bubble detection through the tubing walls. Contactless non-invasive sensors do not need to be replaced after use, only a new tubing set must be inserted into the sensor before the next cycle starts. Additionally, there is no need for expensive and time-consuming cleaning procedures for the sensor, which is very efficient for the workflow, and also underlines corporate sustainability strategies.

Ultrasonic flow meters can measure real-time flow rates with an accuracy of up to 1%, or better at lowest flow rates. Therefore, the CPP flow rate can reliably be measured in the early stages of process development, as well as in large-scale GMP manufacturing facilities. Whenever liquid media is processed, added, or removed within upstream and downstream processes, non-contact flow meters should be implemented to monitor volume and flow rate of the media. If any deviation occurs, the process can be corrected at an early stage, preventing downtime or process failure.

Centralised Data Monitoring to Achieve Process Stability

A QbD strategy requires a deep knowledge of the technical processes, its variables, and the influence of the variables

on the process. Implementing reliable measurement technology, which can be used to track, control, and predict process parameters, is an important part of the strategy. To validate the whole process from upstream to downstream, performance data should be analysed centrally using specialised data management tools and software, which is the second part of the strategy. Leveraging the valuable bioprocess data is crucial to meeting the challenges of modern biopharmaceutical operations in a QbD strategy.

The use of latest sensor technology and continuous data monitoring goes along with the digital transformation within bioprocess manufacturing, which can fundamentally change workflows in process development and production. By connecting instruments and equipment, the entire work process can be operated remotely. Process engineers have a complete overview to monitor each single process step and take action, if needed. Hence, the uptime and productivity of the entire process can be enhanced. Consequently, any process improvement ranging from consistent monitoring of CPPs and validating CQAs, to digital workflows, can help to make processes more stable and increase the process quality.

Considering the hardware perspective of the previously described example with ultrasonic flow meters, the sensors can be connected via an Ethernet gateway to a PLC controller. Depending on the type of gateway, a certain number of flow meters can be monitored and controlled in an Ethernet-based system. The widely accepted Ethernet/IP protocol allows fast and reliable communication and data exchange between the sensors and the PLC. By implementing a pre-configured gateway provided by the sensor manufacturer, companies can rely on a number of standard parameters and commands, which they can choose according to their application requirements. By default, the measured flow rate and volume of each installed flow meter is available to the PLC in real-time. In this manner, process data is continuously collected and can be validated in specialised software tools to ensure that the defined CQAs are achieved.

Data Analysis for Advanced Process Development and Control

Process data is not only important to monitor and control CPPs in biopharmaceutical production, but also in early development stages when processes are designed and later on when it comes to scaling up and process intensification strategies. Leveraging early process data for modelling purposes can lead to faster product development and accelerated time-to-market. Process data helps to scale-up or down processes according to the manufacturing facilities, for example at different sites of a CDMO. In order to successfully perform those models, a deep understanding of the selected processes is necessary. The collected data must be validated, dependencies must be determined, and algorithms must be developed to build and enhance different process models along the production cycle.

Conclusion

The introduction of PAT in bioprocesses is closely connected to a number of monitoring and validating tasks (i.e., critical process parameters and critical quality attributes). The latest sensor technology, which has no impact on the physical and chemical process parameters, should be installed at all relevant process steps to consistently gather process data. Continuous data monitoring and validation at each process step are essential to achieve the defined CQAs. Process data used in a real-time data monitoring and control approach as part of a QbD strategy can lead to reliable and stable processes, highest product quality, and maximum product yield in biopharmaceutical manufacturing.

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