

# Consistency and Repeatability Through Accurate Measurements



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Consistent and repeatable batch operations are key to productivity in pharmaceutical and biotech processes. But obtaining repeatability, batch after batch, remains elusive in the industry according to a recent survey by Pharmaceutical Manufacturing. In many cases, this problem can be mitigated or eliminated by careful attention to measurement and control of fundamental process parameters such as temperature, pH, dissolved oxygen (DO), pressure and flow.

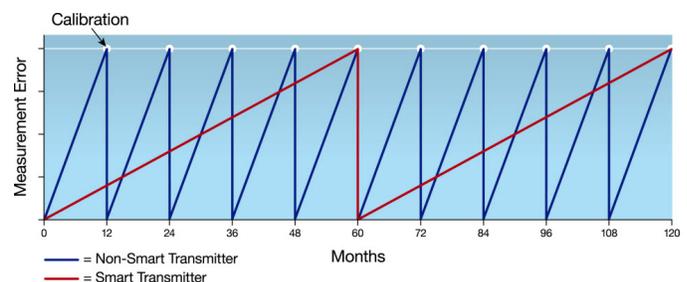
This white paper explores how typical pharmaceutical and biotech manufacturing batch operations depend on fundamental process parameters. It shows the importance of precision and repeatability, and describes how reliable, accurate instrumentation allows automation to support quality and productivity strategies such as the process analytical technology (PAT) initiative, continued process verification (CPV), and the ICH Q10 Pharmaceutical Quality System. It includes information on how to select and specify instrumentation and systems that can improve batch repeatability, quality and productivity.

## State of the art

An electronic survey of process and operations professionals in pharmaceutical and biotech manufacturing was conducted in November 2015 by *Pharmaceutical Manufacturing* magazine to identify application trends and challenges in process measurement. One theme that echoed throughout the study was respondents' desires to assure batch after batch repeatability, a gold-standard performance and quality metric for the industry. Surveyed professionals recognized measurement accuracy, batch repeatability, quality and process efficiency as the most important factors affecting their decisions on process instrumentation.

Instrument accuracy and repeatability directly influence process efficiency – the quantity of in-specification production achieved per unit time and/or cost. Accurate and repeatable basic process measurements such as temperature, pressure and flow support the control necessary

to achieve tight specifications for higher-level parameters such as pH, conductivity and dissolved oxygen (DO), as well as product composition, structure and efficacy. Smart measurement instruments with high stability will maintain required accuracy and repeatability longer and need fewer calibrations. These instruments also provide early notification and identification of problems.



Manufacturing efficiency is directly related to measurement drift.

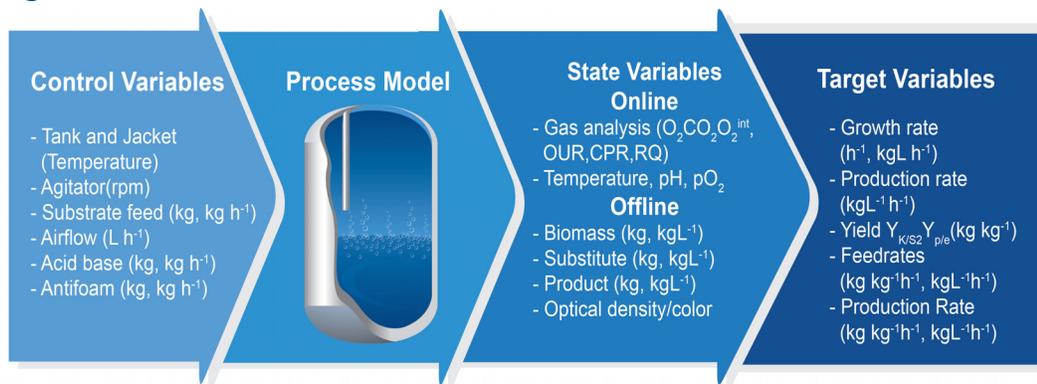
Being able to rely on basic process measurements can reduce reliance on off-line analysis and improve the timeliness of corrective actions that can reduce lost batches and improve productivity.

## Process control of bioreactors

For example, consider cell culture processes such as those used to produce monoclonal antibodies (MAB) like Bevacizumab or Avastin. The bioreactors must provide the conditions that allow the microorganisms to develop their optimal catalytic activity. Control depends on exact and continuous information about physical variables (temperature, pressure, power input, turbidity, and viscosity), biological variables (content of proteins, DNA) and chemical variables (pH value,  $O_2$ ,  $CO_2$ , redox potential) of the process medium, as well as  $O_2$ ,  $CO_2$  and other pertinent components of the exhaust gas.

Poorly controlled pH or conductivity of a cell culture process in a bioreactor (Figure 1-1) may affect the molecular structure of the proteins – if the specified pH range is 6.8–7.1 and the process runs at 6.6, the cells may look correct, but the molecules may have the wrong secondary and tertiary structures, so the biologic functionality is not realized.

Figure 1-1. Bioreactor



Even a small deviation of 0.1 from the optimal pH can significantly affect culture growth and metabolism. Cell culture media usually contains sodium bicarbonate as buffering agent, and pH is usually tightly controlled with a combination of  $CO_2$  sparging to reduce pH and base addition to increase it. Measurements of reactor and sparge gas pressure, and the flows of gas and base solution, must be accurate and repeatable.

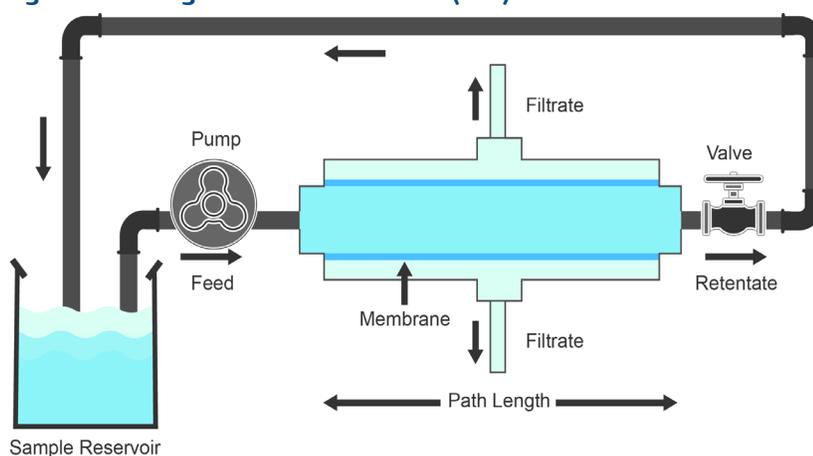
Temperatures must also be held precisely, typically  $\pm 0.2$  °C, and may be shifted, (i.e. from 37 °C to 30–35 °C) after some period of time to keep cells healthy and generating. Temperature measurements must be both accurate and dependable, and heating/cooling flows must be closely controlled.

Dissolved oxygen is typically controlled at a specific set point, usually between 20–50% of air saturation to prevent dissolved oxygen limitation and excessively high dissolved oxygen concentrations that could lead to cytotoxicity. Even though cell growth might be insensitive to dissolved oxygen over a broad range, the dissolved oxygen level may significantly affect product quality and must be accurately controlled.

## Maximizing yield at filtration

In tangential flow filtration (Figure 1-2), two of the important variables are transmembrane pressure (TMP) and crossflow velocity (CF). The TMP is the force that drives fluid through the membrane, carrying along the permeable molecules. The CF is the rate of the solution flow through the feed channel and across the membrane. It provides the force that sweeps away molecules that can foul the membrane and restrict filtrate flow.

Figure 1-2. Tangential Flow Filtration (TFF)



Fluid is pumped from the sample reservoir into the feed port, across the membrane surface (crossflow), out the retentate port and back into the sample reservoir. The crossflow sweeps away larger molecules and aggregates that are retained on the surface of the membrane, preventing gel polarization (the formation of a concentrated biomolecule layer on the membrane surface that can foul or plug the membrane). Liquid flowing through the narrow feed channel creates a pressure drop between the feed and retentate ports. This pressure, which is applied to the membrane, can be further increased by raising the crossflow rate or by restricting the tubing at the retentate port.

Liquid that flows through the membrane (filtrate or permeate) carries molecules smaller than the membrane pores through the filter. The trick to using TFF effectively is to regulate both the TMP and crossflow rate to prevent membrane fouling, thus allowing a greater volume of product to be processed in the least possible time. Both rise together, and poor control leads to membrane fouling, extended filtering time and lost product or yield. Product that remains on the membrane cannot be recovered.

## Best practices rely on instrumentation

Along with quality production, accurate and reliable instrumentation is needed to support best practices including the United States Food and Drug Administration (FDA) process analytical technology (PAT) initiative, continuous process verification (CPV), and the ICH Q10 Pharmaceutical Quality System.

The PAT directive is a “system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.” Although originally conceptualized for small molecule manufacturing processes, it is increasingly being extended to biological processes, which are inherently more complex.

CPV has been adopted and is expected to become mandatory since it was recommended in the FDA Process Validation Guideline issued in 2011. Current CPV practice is mostly manual, univariate and post-production, but is being automated and

extended to multiple variables in real time using reliable instrumentation and online, multi-variate data analysis (MVDA) software. The MVDA platform incorporates built-in model generation tools to combine evaluation of historical batches (post completion) with fault detection and quality projection (in real time) to detect deviations, notify operators, diagnose potential causes and recommend actions to save batches, improve quality and increase productivity.

ICH Q10 describes “a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System.” One of its major objectives is to establish and maintain a state of control: “To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes.” Several key elements of ICH Q10 align with CPV, including knowledge management, which ICH Q10 considers one of its two key enablers (the other being risk management) and is defined as a “systemic approach to acquiring, analyzing, storing and disseminating information related to products, processes and components.” Section 3 of ICH Q10 describes continual improvement of process performance and product quality, saying, “The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.”

PAT, CPV and ICH Q10 guidelines call for consistently collected and easily accessible data. Control system data historian and electronic batch record systems can support this functionality only if they record accurate process data from reliable instrumentation.



PAT encourages a better understanding of process by identifying relationships between parameters and reproducibility, culture performance, and product quality attributes.

## Deviation monitoring and validation of changes

CPV and ICH Q10 include the concept of deviation monitoring, which only works if process data is accurate over multiple batches and stored where it can be referenced from batch to batch. Keeping data together can help ensure that excursions are identified and the associated data can be trended, so reports can be generated from a single source. This requires a deviation monitoring system with the flexibility to report issues and support investigation.

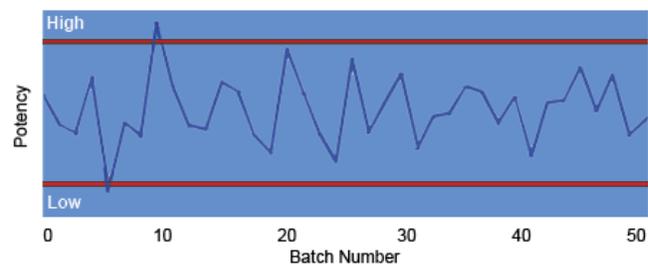
The deviation monitoring system should include the appropriate data fields and reporting mechanisms to reduce the effort expended on data mining. It should be made available to the plant MES to allow real-time documentation and reconciliation of issues as manufacturing occurs. To make this possible, it's important to evaluate the deviation process workflow. Does the system require a minimum number of fields to be populated before a record can be saved (and therefore receive an identification number)? If so, are those fields appropriate for receiving data from an MES to have successful reconciliation?

Many companies already have strong process monitoring initiatives, but not all of them tie back to the validation program and have the appropriate quality oversight. The goal is to combine process monitoring data with the validation program to comply with CPV requirements and derive business and process benefits. The CPV program should be maintained in alignment with the master validation plans for each site and/or process. If the output of the monitoring program is provided to the quality unit and other validation roles as part of a formal review program, it can become a robust mechanism to identify improvements and obtain agreement on implementation of changes. This approach also supports time synergy: Plants can make improvements timed with permits from government agencies with analytics that prove the proposed changes don't cause other changes in the product.

## Batch repeatability

Seek temperature, pressure and flow transmitters that meet and exceed accuracy specifications, are reliable and maintain their accuracy over extended periods of time. Furthermore are equipped with self-diagnostics to alert operators they need calibration or maintenance.

The right instruments giving the right data supports data integrity, the foundation of efficient manufacturing. Build on it with a control system capable of aggregating and analyzing process data to create batch models that can be used to improve efficiency and productivity, and to detect batch deviations before quality is compromised.



Variations between batches that cause deviations lead to spending additional time on extensive analysis, either in real-time or post-time process, to identify how to control and minimize variation in the future to improve quality and yield.

## Conclusion

It's clear that pharmaceutical manufacturing batch operations can be made more consistent, efficient and trouble-free if they're equipped with accurate, reliable instrumentation and empowered with transmitters, control systems and software that support continuous process verification.

Seek temperature, pressure and flow transmitters that not only meet accuracy specifications, but also are certified to maintain accuracy for extended periods of time (stable) and, where appropriate, are equipped with self-diagnostics to alert operators they need calibration or maintenance. To ease installation and reduce paperwork, select instrumentation that is factory calibrated, documented and certified for compliance.

The right instruments giving the right data supports data integrity, the foundation of efficient manufacturing. Build on it with a control system capable of aggregating and analyzing process data to create batch models that can be used to improve efficiency and productivity, and to detect batch deviations before quality is compromised. Integrate control with smart instruments and an asset management system (AMS) to notify operators of anomalies, support drill-downs and diagnostics, and recommend corrective actions. Discover instrument issues before the next batch, and have maintenance correct them before product is compromised.

Measuring and controlling variability with smart process instruments and batch analytics can satisfy the concerns of pharmaceutical and biotech manufacturing professionals by empowering plants to meet tighter set points while ensuring all product is in range and uniform within a batch, and batch after batch.

For more information on Rosemount hygienic products, see [EmersonProcess.com/Hygienic-Solutions](http://EmersonProcess.com/Hygienic-Solutions).

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