White Paper

INGOLD
Leading Process Analytics

OOS? – Stay Within the Limits
with Intelligent Measurement Solutions

Process analytical measurements are playing an increasing role in the production of pharmaceuticals. New developments in measurement technology are improving analytical system efficiencies and keeping a wide range of processes operating within required specifications. To leading-edge sensing systems, METTLER TOLEDO has integrated Intelligent Sensor Management (ISM®) technology. ISM is an innovative platform that has transformed sensor handling and maintenance operations. For the pharmaceutical industry, measurement solutions with ISM are reducing out-of-specification conditions, increasing batch-to-batch consistency, simplifying regulatory compliance, and expanding data transparency.

Introduction

If not corrected promptly, out-of-specification (OOS) conditions in biopharmaceutical manufacturing can result in time- and resource-consuming reprocessing at best, and batch loss at worst. The optimal strategy when dealing with OOS is therefore to minimize the chance of it occurring.

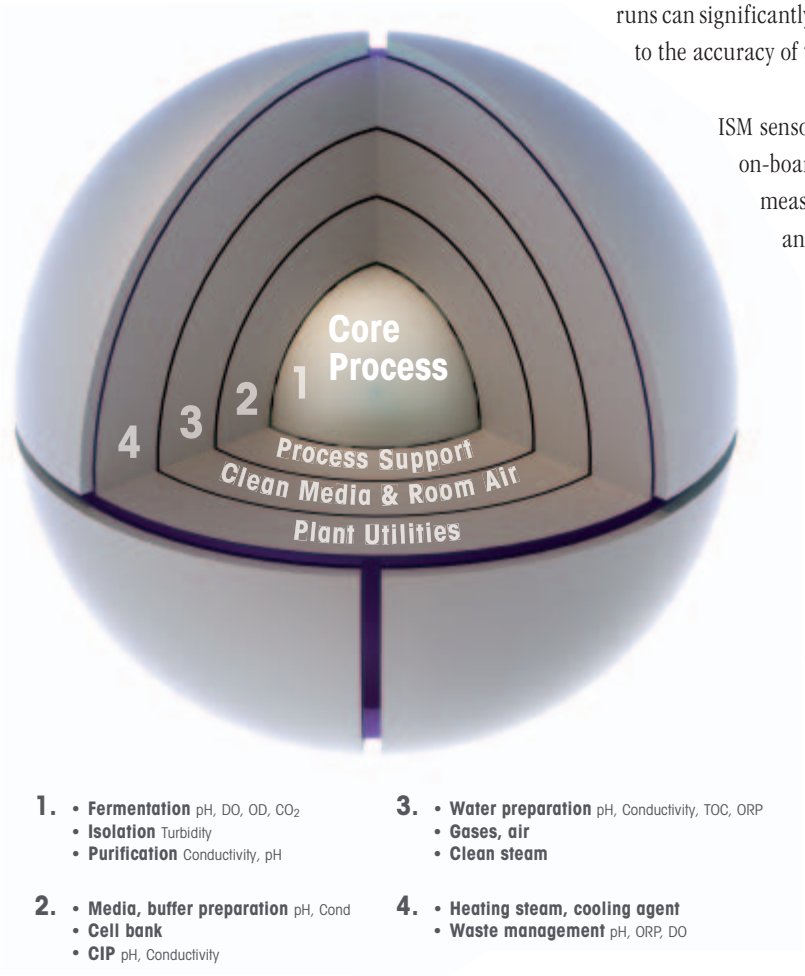
Process analytical instrumentation has been utilized in the production of pharmaceutical products for many decades. In relation to biopharma, analytical sensors are usually installed to monitor and control critical parameters on bioreactors to help ensure process conditions remain within specifications. But the advantages of employing process analytics has spread well beyond fermentation and now includes downstream operations such as purification; and auxiliary processes including buffer preparation, Clean-in-Place, sterilization, pharma waters production, and wastewater treatment.

Advances in process analytics means that modern systems supply more than just a measurement. Digital technology integrated into sensors allows a number of features such as sensor diagnostics, calibration in a lab instead of at the measurement point, robust digitized signal, and electronic documentation of data.

For pharma companies, these features translate into greater convenience in sensor operations, and higher process integrity wherever such systems are used, whether it be in monitoring bioreactors or ensuring water systems comply with regulatory standards.

METTLER TOLEDO

This white paper examines how leading-edge analytical systems can be deployed throughout a pharmaceutical facility from core processes to vital plant utilities, and at each level help increase efficiency, reduce costs, meet regulatory requirements, and ensure that the processes remain within specifications.



Digital signal

Traditional measurement systems send a sensitive analog signal to a transmitter, which converts the signal into a displayed value. Electrical interference caused by surrounding equipment, the presence of moisture in the environment, and long cable runs can significantly degrade the signal causing uncertainty as to the accuracy of the displayed measurement.

ISM sensors operate differently. An ISM pH sensor's on-board microprocessor converts the analog measurement signal into the actual pH value and conveys this digitally to the transmitter and process control system. Being digital, the signal is immune to interference from electrical fields and moisture, and remains stable even over lengthy cables. With ISM, technicians can be assured that the measurement value registered in the process is the same as the one shown on the transmitter or control system display.

Sensor diagnostics

A significant problem in fermentation operations is uncertainty as to whether a sensor will perform dependably throughout a run. Failure of a probe during fermentation may necessitate time-consuming grab sampling and lab measurements, and delayed results can lead to OOS conditions in the reactor.

Intelligent Sensor Management

METTLER TOLEDO's Intelligent Sensor Management (ISM) platform was developed to simplify analytical sensor operations and improve sensor performance for major process parameters, including pH, conductivity, dissolved oxygen, and total organic carbon.

For pharma companies the world over, the features of ISM-equipped sensors and transmitters have led to reduced incidences of OOS conditions, easier regulatory compliance, and greater data transparency. ISM sensors provide analog to digital measurement signal conversion, Plug and Measure start up, data storage, and diagnostics algorithms all of which bring tangible benefits to a wide array of facility operations in pharmaceutical production.

ISM solves this by providing predictive sensor diagnostics. ISM sensors monitor their own condition and through tailorable algorithms predict when they will require calibration, other maintenance or even replacement. This data, displayed as easy to read tools, is available on the transmitter and can be transferred to the process control system. It is also viewable on sensor management software (iSense Asset Suite). By monitoring the diagnostics, technicians can be confident that a "healthy" sensor will perform reliably over the batch run.

Predictive sensor diagnostics are valuable wherever ISM sensors are utilized. They convert sensor maintenance from being a passive, costly and sometimes unnecessary activity, into a fully proactive, safe and controlled procedure. The combination of sensor diagnostics and digital signal greatly enhances process integrity.

Secure calibration

Analog measurement systems require that calibrations be performed at the measurement point, as a sensor's calibration data is retained in the transmitter it is connected to. Calibration is a lengthy process that necessitates calibration materials (e.g., pH buffers) being brought to the measurement point, which carries contamination risks.

With ISM, the microprocessor in the sensor head retains the calibration data, not the transmitter. This means that an ISM sensor can be connected to any compatible ISM transmitter, and more significantly, allows calibration to be performed away from the process in a convenient location such as a lab. iSense Asset Suite, the companion software for ISM sensors, runs on standard PCs and laptops. After connecting an ISM sensor to the computer, it can be accurately and securely calibrated with iSense. Once calibrated, the sensor can be stored until it is required. When connected to an ISM transmitter, the calibration data on the sensor is automatically uploaded and the transmitter configures itself automatically without any operator intervention. This Plug and Measure feature reduces human error and significantly curtails the time a technician spends at a measurement point.

Electronic documentation

iSense is not only useful for sensor calibration and displaying diagnostics: With iSense, a record of a sensor's calibration and maintenance history is automatically stored in the software's database. Additional information such as maximum temperature exposure, operating time, number of CIP / SIP cycles, etc. are also uploaded from the probe to iSense. All this data can be documented electronically or printed as a PDF, enabling the processing of a sensor's history to satisfy regulatory requirements.

Improved reliability and efficiency

ISM's features outlined above not only simplify sensor handling and maintenance, they also improve the reliability and efficiency of operations across a pharmaceutical facility, and reduce the incidence of OOS conditions arising, as shown below.

Core processes

• Fermentation, cell culturing

pH is identified as a critical process parameter in fermentation and cell culturing because enzymatic activities and cellular metabolism are sensitive to pH changes. Therefore, pH levels should follow a pre-defined path to help maximize process yield and minimize OOS. In-line pH measurement has been common for many years but is not without its risks. As mentioned above, should the sensor fail during a batch, pH must be measured using off-line samples (if a redundant measurement is not available), which can be a source of contamination, delivers a less accurate value, is labor intensive, and has an inherent time delay. Checking ISM's predictive diagnostics before a batch ensures that any required sensor maintenance is identified days or even weeks in advance.

Cell cultures require oxygen for the process of energy production from fed nutrients, e.g., glucose. As oxygen has low solubility in water, air flow into the reactor should be carefully regulated to ensure a sufficient level of dissolved oxygen is always present. Overrunning air compressors can severely impact cell metabolism, and also represents unnecessary use of energy.

Controlling the air compressor based on dissolved oxygen (DO) measurements makes certain that the required level of oxygen is supplied at all times. The pO_2 value is traditionally monitored with an amperometric, membrane-covered electrode (Clark type). These sensors require regular maintenance in the form of adding fresh liquid electrolyte and exchanging the inner membrane body. They must also be polarized for up to six hours before calibration. In addition, measurements from amperometric probes are prone to drift over a fermentation batch.

Today, optical DO sensors are available which offer much lower maintenance. They do not use a membrane body or electrolyte, and polarization is not required. Low maintenance is not their only advantage: A consequence of the optical measurement technology is that these sensors exhibit very low drift and therefore are ideal for lengthy fermentation processes.

The level of dissolved carbon dioxide during mammalian cell culturing can affect cell viability and is therefore often monitored and controlled. High pCO_2 levels can inhibit growth and metabolism and therefore negatively impact protein product quality characteristics.

In fed-batch mode, the dosing of glucose-containing nutrient can be controlled by a CO_2 measurement system. METTLER TOLEDO's CO_2 sensor works on a potentiometric principle: CO_2 from the process diffuses through a membrane, and the pH change in the internal electrolyte correlates to the partial pres-

sure of carbon dioxide. The simplicity of this technique is one reason for the sensor's high reliability.

METTLER TOLEDO's CO_2 and optical DO sensors deliver all the advantages of ISM technology, including robust digital signal and CIP/SIP counter. To simplify scale-up, the same model of sensor can be deployed from bench top reactor to full-scale production vessel.

• Purification

Downstream unit operations involve recovery steps that isolate the protein product, and steps for removing impurities to the required level. The process is typically designed in three stages: capture, purification (chromatography) and polishing, each with a distinct purpose. Steps for product concentration and virus inactivation are also part of purification.

The most commonly used sensors for controlling chromatography are pH, conductivity and light absorbance (UV). These probes are usually installed in the inlet and outlet of the chromatography column. The performance of the gradient, the loading of the column, the regeneration, and reequilibration can be checked with conductivity and pH measurements.

Accurate pH control is vital to successful chromatography; even minor variations in pH can prevent clean isolation. In addition, a change in pH of only 0.1 can affect a protein's solubility and potentially lead to a column blockage. Chromatography is a very expensive process step; therefore, utilizing high accuracy pH probes is advantageous for preventing OOS. Employing METTLER TOLEDO ISM pH sensors with their robust digital signal and pre-calibration feature means chromatography integrity is very high. Moreover, the database in iSense Asset Suite provides sensor traceability for regulatory compliance.

InPro 6860i DO, InPro 3250i pH and InPro 7100i conductivity sensors

Process support

• Buffer preparation

The main purpose of buffers in chromatography is to produce and sustain a set pH and ionic strength (conductivity). Buffers are prepared by dissolving chemicals in pharmaceutical grade water, followed by pH adjustment in a mixing vessel. Correct preparation of buffers is crucial for obtaining reproducible and consistent chromatography results, as low buffer accuracy leads to poor separation of molecules and band broadening. In buffer preparation, some key factors must be considered, including the negative logarithm of the acid dissociation constant (pKa) of the buffering ion and analyte, as well as the molarity of the acid and alkali used for pH adjustment.

The high measurement accuracy and fast response of METTLER TOLEDO sensors, coupled with ISM, provides extremely reliable pH and conductivity measurement solutions.

• Clean-in-Place (CIP)

CIP systems have become standard in pharmaceutical production facilities, particularly for those regulated by good manufacturing practice (GMP). The principal objective of a CIP system is to achieve the desired cleanliness of process equipment without disassembly.

The chemical used in CIP is often sodium hydroxide, which is stored in high concentrations to save transportation costs and storage space, and is later diluted. Sodium hydroxide concentration in CIP cycles is around 2 to 5 %. Dilution needs to be determined with sufficient accuracy to ensure solution concentration

Total Organic Carbon Sensor 5000TOCi

is within the required range, and this is best achieved with in-line measurements of conductivity.

Due to ISM's Plug and Measure feature, conductivity sensor installation on water systems is fast and error-free. ISM's digital signal transmission is highly dependable in high moisture processes such as CIP.

After sodium hydroxide treatment, the whole loop must be rinsed with pharmaceutical grade water to make certain that all chemicals are out of the system. This can be monitored and controlled using conductivity and total organic carbon (TOC) measurements. For a CIP process to be deemed effective and complete, the overriding premise is that the water quality exiting the system on the final rinse must be of the same quality as the water entering the system. If the system utilizes Purified Water (PW) or Water for Injection (WFI) at the points of use, then the determination of a complete and final rinse means that the quality standards for PW and WFI must be met.

METTLER TOLEDO's on-line TOC sensors with ISM provide continuous, real-time monitoring of water quality. Operators know immediately when a vessel has been sufficiently rinsed and meets specifications for the specified water purity, preventing over- or underuse of PW or WFI. Diagnostics monitor the condition of the sensor's inlet filer and UV lamp, and inform operators as to when calibration will be required.

Clean media

• Preparation of pharmaceutical grade water

A supply of pharmaceutical grade waters is essential in most pharma production unit operations, for use either as a raw material, solvent, ingredient, reagent, or cleaning agent. PW, HPW, and WFI for biopharmaceutical processes are produced on site from the local water supply.

M800 multi-parameter transmitter

Most biopharmaceutical companies have invested considerable capital in state-of-the-art instrumentation, purification equipment, storage and distribution loops, and also in the calibration and certification of their water systems. Once the water system is installed, qualified, and validated a preventative maintenance and calibration program must be put in place, as calibration of the measurement parameters is required by the pharmacopeias. Periodically, the relevant local or international authorities will inspect a facility's pharmaceutical water generation systems to ensure they are in compliance with local and/or international regulations. Ultimately, the pharmaceutical company is responsible for validation and ongoing calibration of the water system to make sure that it meets pharmacopeia specifications and will pass an inspector's audit.

Increasingly stringent pharmacopeia requirements and the introduction of new initiatives such as Process Analytical Technology (PAT) and Quality by Design (QbD), place added challenges on pharma companies. ISM offers advanced process control to simplify the achievement of PAT and QbD goals, and to ensure the quality of biopharmaceutical waters at all times.

For conductivity and associated temperature determination, METTLER TOLEDO sensors with ISM technology store unique factory and calibration data. Measurement accuracy is increased with in-line calibratable electronic circuitry within the probe and digital communication with the transmitter. TOC sensors with embedded ISM conductivity sensors save previous calibration and system suitability records, while displaying time to calibration and time to maintenance reminders.

Plant utilities

• Pure Steam

Pure Steam is used for sterilization purposes, primarily at the autoclave and for cleaning piping and tanks. Pure Steam is PW or WFI that has been heated above 100°C and vaporized in a manner which prevents source water entrainment.

The quality of Pure Steam is difficult to assess in its vapor state; therefore, the attributes of its condensate are used to indirectly test its quality. The parameters that must be tested are the same as those for WFI, i.e. bacterial endotoxins, TOC, and conductivity. METTLER TOLEDO ISM conductivity and TOC sensors help a facility ensure the quality of Pure Steam is always within specifications and therefore is compliant with pharmacopeia regulations. Predictive diagnostics provide advance notification of maintenance, eradicating unplanned downtime due to sensor failure.

• Wastewater treatment and water reclaim

Biopharmaceutical facilities produce a high volume of wastewater. Water from fermentations usually contains genetically modified organisms as well as DNA, RNA, tRNA and traces of therapeutic proteins, and must undergo treatment before being purged into the municipal sewer system.

In primary treatment systems, organics in water are inactivated by heating (thermal inactivation) or exposure to extreme pH shifts by alternately adding acid and base to cause cell lysis. In most cases this treatment is all that is required; however, due to the cost of pharma waters preparation, an increasing number of facilities are instituting reclaim, recycle and recovery systems. For pharmaceutical use, reclaimed water must pass through a number of purification stages that are monitored via analytical measurements including TOC. High sensitivity of sensors and reliability of displayed measurements are central requirements. ISM's on-board calculation of parameter value and digitized signal safeguard measurement integrity.

Secondary wastewater treatment comprises biological systems for processing primary wastewater effluent. The main goal of secondary treatment is to remove soluble pollutants from wastewater via biological oxidation of organic matter. Secondary biological treatment requires the availability of a large quantity of microorganisms, good contact between these organisms and the organic matter, availability of oxygen, sufficient quantity of nutrient, and adequate time for the organisms to do their work. To ensure a favorable environment for the required reactions in biological treatment, pH and DO must be monitored and controlled.

Analytical sensors for wastewater treatment should be durable, resist clogging and coating, and be low on maintenance. METTLER TOLEDO offers pH sensors with a clogging-resistant open reference junction rather than a diaphragm, and DO sensors with PTFE coating. As long cable lengths are normally found in wastewater applications, ISM's digital signal is highly beneficial. Predictive diagnostics tools provide real-time data on sensor condition, reducing maintenance time and costs.

Conclusion

Out-of-specification production consumes the resources of pharmaceutical companies. Real-time measurement data from in-line process analytical systems helps prevent it occurring. To leading-edge analytical sensors designed for the pharma industry, METTLER TOLEDO has added Intelligent Sensor Management technology. ISM's digital sensor signal transmission and predictive sensor diagnostics significantly improve process integrity, and therefore reduce the incidence of OOS even further. These and the other features of ISM are helping pharma companies to increase batch-to-batch consistency, and remain compliant with pharmacopeia and local regulations.

▶ www.mt.com/ISM-pharma

ISM®

Features overview for ISM sensors:

- More precise measurement signal compared with analog sensors
- Advanced sensor diagnostics
- Predictive maintenance functions
- Plug and Measure functionality
- Digital IP 68 connector
- CIP / SIP counter

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