White Paper

INGOLD
Leading Process Analytics

The Easy Way to Reduce Costs in Drug Manufacturing

Pressures on pharmaceutical companies from regulators, governments, and competitors are forcing them to closely examine expenditure. But making cost savings while ensuring the standard of products remains high is problematic. Recent developments in process analytical technology have opened a door to reduced manufacturing costs without compromising product quality.



Introduction

Changes in regulations, increasing competition, and expiring patents are leading to shrinking margins in the pharmaceutical industry. In addition, the rapid rise of healthcare across the developing world is further hurting drug companies as governments try to contain spiraling costs. It is not surprising then that pharmaceutical companies are scrutinizing their expenditures across the value chain.

A significant problem for many drug producers is how to cut manufacturing costs without reducing quality and efficacy of final products. This white paper looks at a technology for in-line analytical measurement systems that reduces the costs of maintenance and regulatory compliance while also decreasing out-of-spec (OOS) production and the need for expensive reprocessing.

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Adopting a risk-based approach

Requirements placed on the pharmaceutical industry to comply with pharmacopeial and governmental regulations tend to stifle any attempts to change processes once the drug development stage is over and a new product has been licensed.

In recognition that this approach is ultimately bad for the health of the populace, the Food and Drugs Administration (FDA) and other regulators have developed and are developing initiatives to shift the paradigm of "blind compliance" to adopting a risk-based approach to drug development and production. For example, the Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives have opened a path to greater efficiency without affecting product quality. The enhanced process knowledge that these initiatives are designed to engender is clearly advantageous to both the manufacturer and the regulatory agencies.

Reduced production costs

The benefits of in-line process analytics over periodically measuring grab samples in the laboratory is universally acknowledged, and pharmaceutical companies significantly gain from the real-time, continuous data, and reduced workload that inline analytics bring. But what is next? What more can in-line analytics do to cut drug production costs?

The answer is digital technology. Replacing traditional analog instrumentation with digital counterparts opens a wealth of opportunities to reduce measurement point maintenance, moderate training of technicians, and simplify regulatory compliance all of which result in cost savings. Further, digital technology offers far greater process reliability, helps minimize the occurrence of OOS and human error, and can increase productivity.

Analog analytical systems

Analog sensors for measuring pH, dissolved oxygen, total organic carbon, etc., transmit a signal that is sensitive to electromagnetic interference, environmental humidity, and long cable runs. This causes uncertainty as to the accuracy of the measurement transmitted to the process control system. Acting on incorrect data can lead to longer processing, reprocessing, or even batch failures.

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

A further issue with analog systems is that it is impossible to tell whether a sensor will perform reliably for the next hour, day, or week without requiring maintenance. In the case of pH sensors, this has led to some pharmaceutical companies replacing old sensors for new ones every time they are used.

Invariably, complying with pharmacopeias and internal SOPs requires a great deal of paperwork. Every time a sensor is sterilized, calibrated, or maintained, details should be documented, which takes up a lot of time and is subject to human error.

Some digital analytical systems have solved all of these concerns.

Why digital is better

Digital process analytics systems such as those with METTLER TOLEDO's Intelligent Sensor Management (ISM™) combine all of the advantages of in-line analysis with the benefits that digital technology offers.

Firstly, ISM sensors feature an on-board microprocessor. This converts the analog signal from the sensor tip into the actual measurement of the parameter 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.

The microprocessor also stores calibration data. This means that ISM sensors can be calibrated away from the process in any convenient location using ISM Core™ software (see below) and then stored until required. Once connected to an ISM transmitter, the calibration data is automatically uploaded and the transmitter configures itself without technician intervention. These pre-calibration and Plug and Measure features greatly reduce the time a technician has to spend at a measurement point, and also removes the risk of human error.

Convenient calibration and documentation

ISM Core, the companion software for ISM sensors, runs on standard PCs and laptops. Once an ISM sensor is connected to the computer via a USB cable, ISM Core can be used for accurate and secure calibration. In addition, with ISM Core 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 SIP/CIP cycles, etc., is also uploaded from the sensor and stored on ISM Core. All this data can be documented electronically or printed as a PDF, enabling the processing of a sensor's history to satisfy regulatory requirements, and simplifying sensor related SOPs.



Fig. 1: Convenient sensor calibration with ISM Core, outside the clean room.

Predictive 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- and cost-consuming grab sampling and lab measurements. ISM circumvents this by providing predictive sensor diagnostics. ISM sensors continuously monitor their own condition and through tailorable algorithms predict when they will require calibration, other maintenance, or even replacement. Before a batch, a sensor can be checked using ISM Core and



Fig. 2: ISM pH sensor

Table 1: Technological comparison between analog and digital pH systems.

	Analog pH system	**Digital pH system**
Sensor	Potentiometric pH sensitive glass getrennt Reference electrode with liquid junction Built-in temperature (compensated) sensor	Potentiometric pH sensitive glass Reference electrode with liquid junction Built-in temperature (compensated) sensor Digital-to-analog converter in sensor head Memory for calibration data Automatic counting of SIP/CIP cycles
Sensor output	mV High impedance Variable resistance for temperature	Digital, one-wire protocol
Cable	Multi-wire Limited length	One wire Up to 80 meters
Transmitter	High impedance mV input Calibration data part of transmitter Output analog HART bus system Simple sensor diagnostics	Digital input Automatic sensor recognition Output analog HART bus system Advanced real-time diagnostics
Calibration	Sensor must be connected to transmitter pH buffer solutions for slope and zero point	Sensor connected to calibration software or transmitter pH buffer solutions for slope and zero point
Sterilization	Typically after calibration, mounted in reactor	Typically after calibration, mounted in reactor

any required maintenance undertaken. This ensures that the sensor will perform reliably throughout the entire run.

Table 1 shows a comparison of analog and digital pH sensors. Both designs feature pH sensitive glass, liquid junction, and a reference electrolyte. The difference in performance and reliability is due to the ISM technology in the digital sensor.

Optical measurement technology

Digital technology is not the only recent advance in process analytics. For determination of dissolved oxygen (DO) levels, optical technology offers significant advantages over traditional polarographic sensors. Firstly, due to the nature of the technique, optical DO sensors are very stable even over long fermentation runs and therefore provide a more precise measurement; and secondly, they are low on maintenance. Instead of the replaceable membrane body, inner body, and electrolyte fluid found in polarographic sensors, only one component of METTLER TOLEDO's optical DO sensors, the OptoCap oxygen-sensing element, requires periodic exchange.



Fig. 3: ISM Core as a report generator

Table 2 compares analog, polarographic dissolved oxygen sensors with digital optical dissolved oxygen sensors.

ISM saves time

Changing from analog to digital technology can be challenging for pharmaceutical companies as the process must be validated and new SOPs require approval. Figure 4 shows the workflow for using in-line sensors whether analog or digital.

Table 2: Technological comparison DO system analog versus digital

	Polarographic DO analog	**Optical DO digital**
Sensor	Reduction current O_2 Anode/cathode separated by semi-permeable membrane Liquid electrolyte	Fluorescence quenching OptoCap with embedded chromophore No electrolyte
Preparation	Pre-polarization of 6 hours	Works out of the box
Sensor output	nA current signal Temperature signal	Digital output RS485
Consumable	Membrane body Electrolyte, periodically	OptoCap, seldom
Cable	Multi-wire Length limited	Multi-wire Up to 80 meters
Transmitter	nA input Polarization voltage output to sensor Calibration is part of transmitter Simple sensor diagnostics	Digital input and power output for sensor Transmitter reads calibration data from sensor Pre-calibration possible with ISM Core software or transmitter Advanced sensor diagnostics
Sterilization	Together with reactor	Precalibration possible with ISM Core or transmitter
Calibration	Typically after sterilization in air saturated media	Typically after sterilization in air saturated media

In Table 3 the "4 steps" for pH sensors are explained in detail and show the benefits of ISM technology. The indicated time savings in Table 3 are on the conservative side. Not calculated is time lost due to correcting OOS conditions. ISM detects an "unhealthy" sensor before installation therefore it can be maintained or, if necessary, replaced before the run.

The example in Table 3 shows a maintenance saving of 45 minutes per batch.

Table 4 shows the "4 steps" for DO sensors. The greatest savings in maintenance costs are achieved if changing from analog polarographic to digital optical measurement. A time saving of 35 minutes per batch for DO measurement is possible. The 6 hours pre-polarization time required for polarographic sensor is not included in this estimation as this does not require operator attendance and often takes place overnight.

Together with the time savings achievable using ISM pH sensors, 70 minutes per batch less maintenance time can easily be realized. At the same time, ISM offers

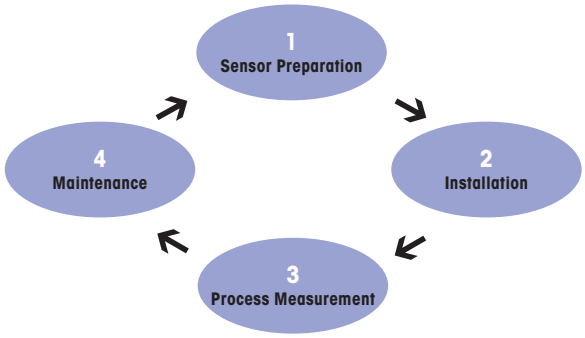

Fig. 4: Four step workflow for in-line sensors in bioprocesses.



Fig. 5: ISM optical DO sensor

Table 3: The four steps for pH electrodes in more detail

Step	Task	Analog pH sensor	ISM pH sensor	Benefit of ISM
1-Sensor evaluation	Visual inspection, performance check	Slope and zero check when connected to transmitter. Check number of SIP cycles in separate sensor records	Connect to ISM Core, check key performance table showing all relevant data incl. SIP cycles	All information on ISM Core, no manual records. Time saving – 5 min.
	Calibration with pH buffers	Sensor connected to transmitter, near bioreactor. Write calibration data to sensor records	Sensor connected to ISM Core in any convenient place (e.g., lab, maintenance shop), Calibration data stored in sensor head and ISM Core database	Convenient and fast. Time saving –10 min.
2-Installation	Mount sensor in housing, connect cable to transmitter	Identical	Identical	
	Sterilize in bioreactor	Identical	Identical	
3-Process measurement	Measurements can begin after sensor cooled down and reactor is filled	Identical	Real-time diagnostics indicate if process calibration is needed before measurements begin	Significant time saving due to less sampling. Time saving – >20 min. per batch
	Process calibration	Fixed schedule, based on experience	Dynamic, only if needed	See above
4-Maintenance	After batch work cleaning, decontamination	Visual inspection, diaphragm cleaning according to schedule	ISM Core indicates need for diaphragm cleaning	Advanced diagnostics indicate need for maintenance. Time saving – 10 min.

Table 4: The four steps for dissolved oxygen electrodes in more detail

Step	Task	Polarographic DO sensor analog	Optical DO sensor with ISM	Benefits of optical technology and ISM
1-Sensor evaluation	Visual inspection	Check anode/cathode, membrane. Exchange membrane according to schedule. Fill membrane body with electrolyte. Assemble sensor. Pre-polarize sensor for 6 hours via transmitter or sensor master	Check if clean no pre-polarization needed	Optical sensor works out of the box saving 15 min. (6 hours pre-polarization time not included)
	Verification, performance check prior to sterilization	Connect to transmitter and perform 1-point calibration in air. Check sensor current. Report data	Connect to ISM Core and perform 1-point calibration in air. All data stored in sensor head and ISM Core database	Convenient location for verification saving 10 min.
2-Installation	Mounting in housing, connect cable to transmitter	Keep disconnected status as short as possible, if pre-polarized with sensor master	Mounting identical	
	Sterilization, together with bioreactor	As described	Automatic switch-off saves OptoCap lifetime during sterilization	
3-Process measurement	Start sparger, wait for air saturation	Perform 1-point calibration (100% air). Write data in sensor records	Perform 1 point calibration (100% air), scaling mode	Calibration data stored in sensor head
	Measurement	Prone to drifting	Almost no drift. Real-time diagnostics indicate issues.	Greater reliability
4-Maintenance	Cleaning, decontamination	Clean anode/cathode	Clean outside of sensor body only. Need for OptoCap replacement is indicated by ISM Core	Time saving – 10 min.

accurate calibration and automatic electronic record keeping of sensor history.

Conclusion

Digital process analytical systems are being adopted by pharmaceutical companies across the world, as they offer improved performance over analog systems. ISM technology provides easier sensor handling, greater process reliability, and simplified compliance; and, as has been shown, it can also significantly cut costs - without compromising product quality.

To find out what savings you can achieve by switching to ISM, visit:

▸ **www.mt.com/ISM-pharma-calc**

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