# Pharmaceutical & Biotechnology

Perspectives in Liquid Process Analytics

# 24 News

**INGOLD**

Leading Process Analytics

**THORNTON**

Leading Pure Water Analytics

## Optical DO Measurement
## Simply Better

**For a large European pharmaceutical group, accurate, low maintenance dissolved oxygen sensors are central to efficiency in their research. The predictive diagnostics, fast start up, and easy servicing of intelligent optical measurement has made it their technology of choice.**


### Global pharma company

Our customer is a leading Italy-based pharmaceutical group. Across 14 manufacturing sites spread throughout the world, they annually produce over half a billion packs of product. For thirty years, the group's biotech division has been a leading center of excellence in biotechnology innovation.

The principal activities at the biotech division's Italian facility are improving cell line productivity, development and validation of analytical methods, and drug production for clinical trials and for the marketplace.

In the cultivation of mammalian cells, scientists at the facility are currently conducting research into maximizing yield through the control of dissolved oxygen levels throughout fermentation.

### Optical sensors are very low on maintenance

For many years, the biotech division had been using DO sensors based on polarographic technology. However, the demands of a long polarization time, high maintenance, and signal drift during extended fermentations were impeding the division's research. This prompted technicians at the facility to contact METTLER TOLEDO for an alternative solution. Our engineers proposed optical technology as a better option.

DO sensors based on optical measurement employ fluorescence quenching to provide oxygen readings. Unlike polarographic

METTLER TOLEDO

probes, optical sensors do not contain a membrane, inner body or electrolyte; elements which require regular replacement. The InPro 6860 i optical DO sensor has only one replaceable part, the oxygen-sensitive OptoCap. Exchange of the OptoCap can be done in a minute and on average is only required a few times a year.

### Minimal drift and no polarization

Low drift is another major advantage of optical DO sensors, and METTLER TOLEDO has reduced drift further by employing Automatic Stability Control in the InPro 6860 i. In addition, optical probes require no polarization, so the InPro 6860 i can be up and running very quickly.

The combination of high measurement accuracy, low and easy maintenance, minimal drift, and rapid startup ideally match the research facility's requirements.

### Predictive diagnostics for measurement confidence

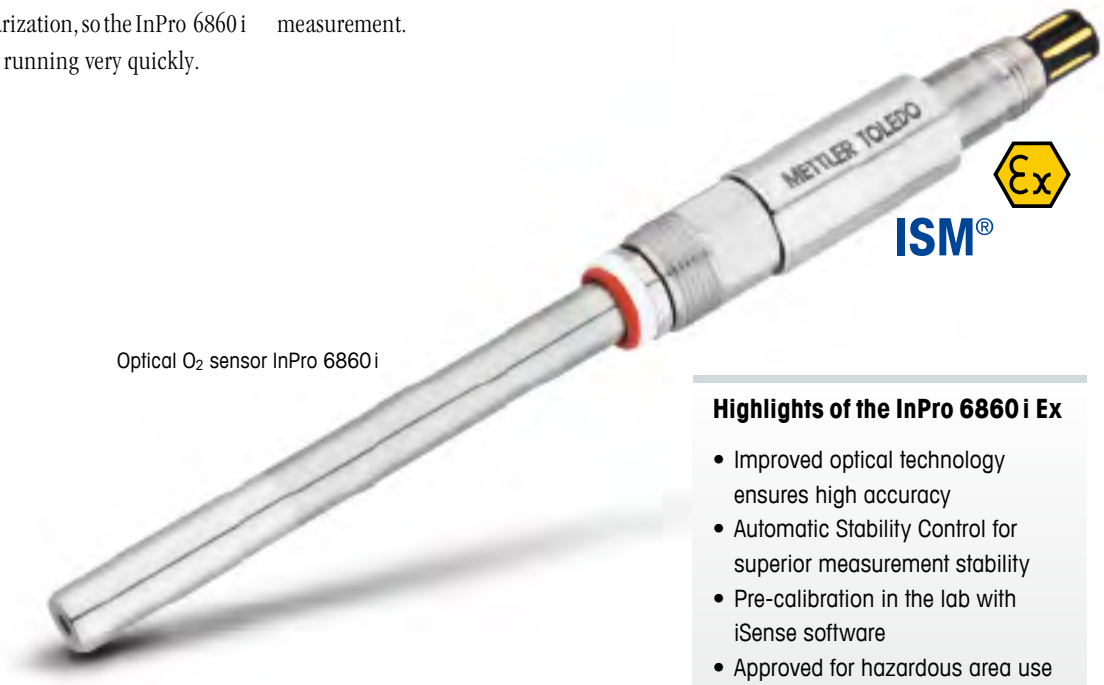
The facility installed three InPro 6860 i sensors along with M400 transmitters which would allow technicians to monitor the sensors' Intelligent Sensor Management (ISM®) predictive diagnostics. These tools provide real-time status information to provide assurance in sensor performance and hence confidence in the DO measurement.

### High satisfaction

Technicians and biotechnologists at the research facility are very satisfied with the accuracy and low maintenance of the METTLER TOLEDO solution and are considering switching all polarographic DO measurements to optical.

The InPro 6860 i is now available with Ex certification (see next page).

► **www.mt.com/ISM-pharma**




Optical $O_2$ sensor InPro 6860 i

### Highlights of the InPro 6860 i Ex

- Improved optical technology ensures high accuracy
- Automatic Stability Control for superior measurement stability
- Pre-calibration in the lab with iSense software
- Approved for hazardous area use

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# Accurate, Low Maintenance DO Measurement in Hazardous Areas

**Optical dissolved oxygen sensors are rapidly replacing amperometric probes. The easy handling and exceptional performance of the InPro 6860 i has made it one of the most successful optical DO sensors available. The addition of Ex certification means it can now be used in hazardous areas.**

### Intrinsically-safe DO solution

Low drift, fast response, and less maintenance are the main reasons why optical dissolved oxygen sensors are becoming increasingly common in biopharma R & D and production facilities. For applications where there is a fire or explosion risk, a sensor with Ex certification is required.

METTLER TOLEDO now offers a unique intrinsically-safe DO measurement system consisting of the M400 2-wire transmitter and the new InPro 6860 i Ex sensor.

### High stability, minimal maintenance

The InPro 6860 i Ex has all the features of the non-Ex version including, digital and analog outputs for compatibility with benchtop bioreactors, high measurement stability thanks to its Automatic Stability Control feature, and a hygienically polished surface finish. Maintenance on the sensor only amounts to periodic replacement of the one-piece OptoCap oxygen-sensing element.

The M400 2-wire transmitter is a single-channel, multi-parameter unit for DO, gaseous oxygen, ph / ORP and conductivity measurement. It is available with HART®, FOUNDATION fieldbus™ and PROFIBUS® PA communication protocols.

### ISM® technology is a major benefit

A key feature of the InPro 6860 i Ex / M400 system is the inclusion of Intelligent Sensor Management (ISM) technology which provides Plug and Measure start up, calibration in any convenient location, and intelligent diagnostics to provide confidence in sensor condition before and during a batch.

► www.mt.com/InPro6860i


### Highlights of the M400

- Wide parameter range includes optical DO
- HART, FOUNDATION fieldbus and PROFIBUS PA protocols
- Compatible with ISM and analog sensors
- Approved for hazardous area use

# New Trends in Process Analytics
## for the Pharmaceutical Industry

**Kurt Hiltbrunner at METTLER TOLEDO is an expert in the deployment and use of process analytical measuring systems in pharmaceutical production. He travels around the globe advising pharma companies on how to improve their processes and increase profitability. Pharmaceutical and Biotechnology News spoke to him about new trends in drug production.**

**Mr Hiltbrunner, what do you see as being the current trends in biopharmaceutical manufacturing and do they affect process analytics?**

I think there are two major trends: the increase in a move towards cell culturing rather than microbial fermentation, and the rise of biosimilars as more and more drugs lose their patent protection.

The production of biosimilars doesn't place any new demands on process measurement systems, but in respect of cell culturing, batch duration is much longer compared with most microbial fermentation processes. Also, ideal growth conditions are in a much narrower range. That means analytical sensors must be very high in accuracy and very low in drift.

**What is the main pain point for pharmaceutical companies regarding cell culturing?**

Obviously, they want to maintain optimal growth conditions during a run as any deviation slows production or lowers yield or protein quality. Typically lab measurements of pH will be made periodically, and if they differ from the measurement coming from the in-line sensor, the problems start. Is the sensor at fault? Does it need calibrating? Or is there something wrong with the lab measurement? As changes to the process are more likely to be based on the in-line measurement rather than that from the lab, technicians want to be as sure as possible that the in-line sensor is operating reliably. Accuracy leads to batch-to-batch consistency.

**Apart from pH, what other analytical parameters are important to monitor during cell culturing?**

Dissolved oxygen is important, as is dissolved $CO_2$, which has sort of been overlooked. $CO_2$ can easily pass the cell membrane and enter the cytosol and the mitochondrial compartment of a cultivated cell. If it does, intracellular pH will change and important cellular processes can be affected. So, keeping $CO_2$ on track can greatly reduce batch time and ensure product quality is high.

**You mentioned dissolved oxygen. Optical DO measurement technology is growing in acceptance. Is that likely to continue?**

Absolutely. Compared with electrochemical sensors, optical sensors are much easier to handle. I think over the next five years the use of optical probes will overtake electrochemical. Validation is slowing conversion but the much lower maintenance of optical will make it the winner.

**Top sensor and instrumentation companies today offer digital measurement systems. Will digital sensors become the accepted standard in the pharma industry?**

Yes, I'm sure that'll happen. The situation with digital systems is similar to that of optical oxygen sensors: the advantages are just too great, and digital sensors will outnumber analog ones in the coming years. Analog-to-digital conversion directly in the sensor provides a robust signal which suffers no interference from humidity and allows longer cable lengths. This is a big improvement in sensor signal transmission.

Beyond signal robustness, digital sensors can offer sensor diagnostics and pre-calibration capabilities, so at the start of cell culturing or fermentation you can be sure the sensor will perform reliably throughout.

**Do digital sensors mean transmitters will become obsolete?**

That's a question I hear many times during customer visits. I think the answer's almost certainly 'no', as it's normally a requirement to have a measurement visible at the process.

Also, digital sensor signals can be integrated into next level control systems, but only if corresponding software for the particular hardware is written. With a transmitter, the full power of digital technology and diagnostics can be easily used. And transmitters can provide outputs in many different formats, from analog 4 – 20 mA to those designed for whatever bus system is being used. Additionally, they can display not just the measuring value but also give relevant information about the current status of the sensor, which is a growing request from customers.

**Cost pressures, which were not such a great concern to the pharma industry in the past, are coming to the fore. How can process analytics help here?**

There have been many developments in process analytics that lower running costs and also make operations easier in pharma plants, and so reduce training and maintenance: multi-parameter transmitters, and the optical and digital technologies we've been talking about are a few examples. Indeed, our Intelligent Sensor Management digital technology can save literally thousands of hours spent on maintenance over the course of a year.

# Highest Sensor Flexibility and Usability
## at Leading Life Science Company

**Pressures on the bioprocess industry are creating greater demands on process equipment. In recognition, Eppendorf has incorporated Intelligent Sensor Management (ISM®) technology into their latest bioprocess control station. The result is a unique system that offers unequalled performance and ease of use.**

### Bioprocess equipment has to improve

As the landscape within the bioprocess industry continues to evolve at record pace, advances in sensor technology remain at the forefront. Process demands for fermentation and cell culture have drastically increased in complexity, driving the need for more sophisticated R&D and production equipment. Increased precision and accuracy of measurements, flexibility between sensor platforms, and advanced quality control will continue to be the most sought after improvements in new product offerings.

### Global life science equipment supplier

Eppendorf is a leading life science company. Through their ever-expanding bioprocess product portfolios and by exploiting the strong synergies in bioreactor technology and polymer manufacturing, Eppendorf has emerged as a global player and valuable resource to its customers in the bioprocess marketplace.

### A universal control station

Developments in the world of sensor technology have not always coincided with developments in the equipment needed for process control. This has left many laboratories struggling to retrofit modern sensors into existing control platforms. Recognizing this challenge, Eppendorf has launched the BioFlo® 320, their newly introduced bioprocess control station. The BioFlo 320 was designed with one goal in mind: to bring the first truly universal control station to the scientists who need it. Central to the performance of the unit is the inclusion of METTLER TOLEDO sensors with Intelligent Sensor Management (ISM®) technology.

ISM is a process analyzer platform that increases measurement system reliability, improves process safety, and significantly reduces sensor handling and maintenance. Eppendorf realized how the advantages of ISM would benefit its customers and were eager to integrate it into their equipment.

### Simplicity and high performance

The addition of ISM in the BioFlo 320 means the need for cumbersome sensor retrofitting has been removed; plus, flexibility has been significantly increased. Users can choose to control their process using any ISM sensor (pH, amperometric or optical DO, dissolved $CO_2$, or redox) without having to think twice about what else is needed. The control station is set up to recognize which sensor is connected and automatically configures the software for use, leaving no work for the operator. The ability to view sensor diagnostics

means any required sensor maintenance can be conducted before a batch, providing high confidence in sensor performance throughout the run.

The universal concept of the BioFlo 320 does not end with the sensors. Incorporating interchangeable autoclavable and single-use vessels, field-upgradeable TMFC modules, bi-directional agitation and peristaltic pump motors, and universal software designed for both microbial and cell culture applications are some of the features that emphasize 'universal design'.

## Flexibility reaches new heights

The combination of ISM with Eppendorf bioprocess control stations offers a new level of flexibility, as Kevin Voll, Product Manager for Benchtop Bioprocess at Eppendorf explains: "Bioprocess is a tremendously complex and diverse field. The ability to meet the current and future process needs of our customers is a top priority at Eppendorf. Sensor flexibility is paramount to the concept of universal equipment design and the integration of the METTLER TOLEDO ISM platform into our bioprocess equipment is a new and exciting step for us. The advent of digital sensors has made it possible to offer in-process flexibility for a range of sensors on a single device."

**www.mt.com/ISM-pharma**


The range of ISM sensors includes pH, ORP, dissolved oxygen, and dissolved $CO_2$


# Ensure Pharmacopeia Compliance
## with Digital Conductivity Sensors

**The conductivity limits of pharmaceutical bulk waters must meet the requirements of the applicable global pharmacopeia. Further, the conductivity instrument itself must comply with calibration requirements to meet all global pharmacopeias. UniCond® sensors not only confirm compliance, they also provide the highest degree of accuracy.**

### The need for better performance

As requirements for pharma waters become ever stricter, so the need for increased analytical measurement accuracy and repeatability has become greater.

The advent of the digital sensor has opened up new horizons for the performance of in-line analytical equipment, and provides benefits in ease of use that non-digital sensors cannot match.

### Digital signal is extremely robust

Traditional analog conductivity measurement systems can be prone to signal loss between sensor and transmitter due to interference to the AC signal.

UniCond sensors operate differently. Signal processing takes place within the probe head itself. Measurements are then sent digitally to the transmitter. Digitizing the analog signal in proximity to the sensing element is a significant improvement, as the robust signal is immune to interference or degradation. High confidence in the reliability of the measurements received at the readout instrument is therefore always assured.

### Major improvement in accuracy

Signal degradation and variance is eliminated with UniCond sensors because of the integrated measurement circuit. Impedance and capacitance problems associated with analog sensors and cable length are eradicated. Further, integrating the sensor and the measuring circuit provides far greater measurement accuracy compared with analog probes.

### Error-free start up

A reliable and accurate digital signal is not the only benefit of UniCond sensors. Intelligent Sensor Management (ISM®) technology means on-board memory stores and communicates complete sensor identification and calibration data to the readout instrument for simplified startup and calibration. The result is convenient Plug and Measure functionality, and greatly reduced chances of operator error.

With conventional sensors, the user must remember to manually enter the precise cell constant and temperature calibration data for each individual probe into the transmitter's memory to achieve rated accuracy. The UniCond's integral sensor eliminates questions about which cell constant to use, calibration data to enter, spare parts to maintain and other decisions where multiple sensor types would normally be required. This significantly improves system simplicity and reliability.

### UniCond for USP compliance

Compliance with USP <645>, EP 2.2.44 and all other global pharmacopeias requires calibration of the sensor cell constant, the measurement circuit, and the transmitter. The measurement circuit in UniCond sensors is traceable to NIST and is calibrated prior to assembly. The cell constant is traceable to ASTM. In addition, UniCond sensors can be calibrated in-line, as recommended by the USP and EP. Also, ISM simplifies regulatory compliance by storing sensor calibration data internally and reducing written record keeping.

▶ **www.mt.com/UniCond**

ISM®

**UniCond conductivity sensor**
**Main benefits:**

- 33 % improved accuracy over analog sensors
- Digital signal ensures high process reliability
- No signal degradation over long cable lengths
- Can be calibrated in-line as recommended by USP and EP

# Flexible Karl Fischer Titration
## of Lyophilized Drugs

**Also known as freeze drying, lyophilization offers a rapid and thorough technique for preserving vaccines and other injectables during storage. The water content determination of lyophilized materials is crucial and not always an easy process as the weight of the lyophilized material may not be known initially. Combining LabX® balance software with a Compact Karl Fischer Titrator, makes this analysis simple and foolproof.**

A Karl Fischer determination of lyophilized materials can be carried out using one of two techniques, i.e. either the entire content of the vial is transferred to an oven attached to a Karl Fischer Titrator or an external extraction is performed. An extraction is preferred, as the vial remains sealed while a solvent is injected into the vial.

The METTLER TOLEDO C30 Coulometric Karl Fischer Titrator is an ideal solution for external extraction with the built-in External Extraction method. The process starts running blank solvent titrations in order to determine the water content in the solvent. To dissolve the sample, the solvent is injected into the vial and then sonicated. A defined volume of sample dissolved in solvent is drawn from the vial and titrated. Prior to the titration, the weight of solvent, sample and injected solution are entered in the C30 for subsequent error-free result calculations.

### The ideal vs. Day-to-day reality

The operator must know the initial weight of the vial and sample for the aforementioned method. Ideally, testing labs should know the weight of the lyophilized sample and the empty vial when they receive it. In this case, the C30 is able to calculate the water content of the lyophilized material automatically.

However, testing labs often do not know the weight of the sample either because their customers do not provide the empty vial weight or because of weight changes in the material (as it is dried) during the lyophilization process. This renders the C30 built in method obsolete and forces the operator to carry out the calculations manually after the titration analysis, introducing extra time-consuming steps, such as cleaning, drying and weighing the empty vial. This manual procedure is also prone to error.

### Simplified and error free workflow

However, calculating the water content of the lyophilized sample without knowing its initial weight is no longer a manual and tedious operation thanks to a new method in LabX balance laboratory software. By connecting the C30 and an analytical balance to LabX software, the cal-


C30 Karl Fischer titrators and LabX software for automated and error-free calculations.

culation is performed automatically after the analysis.

The solution is the tailored LabX balance method that ensures a simple and instructed workflow with error-free calculations. From the first weighing on, the vial, including sample and all subsequent weighing (dried and empty vial) is automatically associated with the initial ID that has been entered or scanned by a barcode reader. LabX automatically calculates the final sample weight and the water content of the sample using the C30 Titrator results. This early identification ensures secure operation during further stages to boost operator confidence and reduce the margin of error.

The LabX balance workflow simplifies the weighing and identification process for the secure and simple water content determination of lyophilized substances where the weight of the sample is not initially known.

Text: Matthew Eby
Product Manager Titration

- **www.mt.com/karl-fischer**
- **www.mt.com/labx**

# Get in-line with METTLER TOLEDO

ISM®


## New! DIN Rail Transmitter

### High Performance in a Minimum of Space

The M100 DR is a compact, versatile and easy to commission transmitter for DIN rail mounting. It is a single-channel, multi-parameter unit compatible with 1-wire Intelligent Sensor Management (ISM®) sensors for measuring pH, oxygen and conductivity.

Ideal for process development environments, the M100 DR provides an easy way of integrating ISM sensors via the HART protocol.

► **www.mt.com/M100**

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