

# Pharmaceutical

Perspectives in Liquid Process Analytics



# 10 News

**INGOLD**

Leading Process Analytics

## New Digital pH and DO Sensors Improve Operational Safety and Optimize Maintenance

**A new enhanced Intelligent Sensor Management System (ISM) concept for digital pH and DO sensors offers advanced predictive diagnostics information for improved handling and maintenance. It opens up the way to optimized maintenance management and advanced process control to save costs and to avoid unexpected downtimes.**

**ISM**



### Digital ISM for improved process

In pharmaceutical plants pH and DO measurement is critical to process control and yield. In addition, higher productivity while maintaining process safety and compliance to FDA standards become ever more important. This means that also process analytical measuring systems not only have to fulfill corresponding validation criteria but also to provide diagnostics information on their status and usability. Easy and safe handling, advanced diagnostics information about sensor status and predictive information on safe use for the next production run are critical for ensuring process safety.

Such information can include the number of sterilization and CIP cycles, sensor diagnosis of diaphragm fouling and ageing of the glass membrane for pH electrodes, or

status of sensor wear for inner bodies of DO sensors.

### Consequences of erroneous pH measurements

In biopharmaceutical processes at the beginning of each batch run, prior to sterilization of the system, pH electrode calibration is carried out using two different pH buffers. Although contaminated diaphragm shows increased resistance, it is often still possible to carry out calibration within certain limits, but there is some considerable risk that during fermentation, diffusion potentials and consequently erroneous measurements and poorly reproducible pH control will occur. This would negatively impact process control and lead to sub-optimal growth conditions and lower yields.



**METTLER TOLEDO**

### ISM for optimal maintenance

The METTLER TOLEDO “Intelligent Sensor Management” (ISM®) system with its advanced diagnostic functions provides help for decisions that repeatedly have to be made before start of a new batch, such as: “Is the pH electrode or the DO sensor still in good enough order to guarantee optimal process control for the whole batch?” If a pH electrode can still be used, ISM provides clear information about increased diaphragm resistances or glass impedances. In highly-sensitive cultures, e.g. mammalian cell cultures, it is normal practice to employ a new electrode for each new batch. The detailed directives can vary from facility to facility and are dependent upon the SOPs in force. In other plants, it is important to be able to know the number of already absolved sterilization cycles for deciding on whether or not to reuse an electrode or a DO sensor membrane or inner body. In such instances ISM delivers the exact current number, together with data on the sterilization temperatures. If specified in the SOP, ISM with advanced diagnostics also supplies information on any impending maintenance of the pH electrodes or DO sensors based on deviations in parameter setpoints.

### Easy and fast replacements through precalibrated sensors

In the case of large bioreactors, such as the 120'000 liter vessels used for antibiotics production, in-situ calibration of the pH electrodes is mostly a quite complicated task. Since the transmitters and housings are only accessible via outer gantries, it is difficult to handle distilled water, buffer solutions and electrodes, and a lot of practice is required to perform a correct calibration. Thanks to ISM, such procedures are now a thing of the past. Pre-calibration of the electrodes can be carried out at ease in the plant laboratory with a PC-based calibration tool under ideal conditions, and furthermore, as no particular time factor is involved, free of stress. If there is an urgent need for a replacement electrode, a new one can be made available directly off the shelf. This pre-calibrated electrode is simply installed through automated sensor recognition and transmitter configuration and measurement can be resumed immediately. For DO sensors, pre-calibrated sensors can be stored pre-polarized to offer a seamless and fast replacement.

### Digital sensor offering

METTLER TOLEDO has expanded its offering to pH electrodes and DO sensor families

- InPro 3250 i/InPro 3253 i
- InPro 4260 i/InPro 4800 i
- InPro 6850 i

to include digital ISM technology. These intelligent sensors will all be available with ATEX and FM approval, and the sterilizable sensors of the InPro 3250 family are in addition also certified to EHEDG standards.

### Benefits of digital communication

The digital communication between sensor and transmitter ensures undisturbed data exchange, leading to greater process reliability and efficiency. The data exchange is not only insensitive to spurious interferences but also the cable connection length between the sensor and transmitter can be considerably extended.

### Highly suitable for validated processes

Users of ISM technology in conjunction with the transmitter M 700 have an FDA-conform protocol, the so-called “Audit Trail”, at their disposal. A coded, manually unalterable logging file allows traceability of when and by whom changes have been made. Password-protected user-hierarchies enable staggered access rights to the transmitter to avoid accidental

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#### pH and DO sensor status data:

- Full sensor specifications
- Sensor wear monitor
- ONtime, pH glass and references impedances, CIP/SIP counter
- Min/max. temperatures and pH/DO-values during measurement
- Calibration data and history

#### Convincing customer benefits:

- Simple, robust connection
- Disturbance-free measurement
- Easy setup through “Plug & Measure”
- Forecast of calibration and replacement intervals
- Password-protected settings
- Identification of all users
- Early detection of possible failure through predictive diagnostics

changes to settings. The sensor status data are also included in the ISM package. All relevant characteristics are stored permanently in the sensor and contain sensor specification data as well as variable data such as actual sensor wear, highest reached temperature or pH and DO values. This feature is particularly beneficial when evaluating the actual measurement conditions and estimating the expected life of the sensor.



[www.mt.com/ISM](http://www.mt.com/ISM)

## Ensuring Safety in Reactor and Centrifuge with Oxygen Gas Monitoring System

**Critical reaction and extraction stage in an API production process can be ensured safe with online gas-phase oxygen sensing technology which eliminates time-consuming sampling hassle.**

### **Divis Laboratories Ltd., India**

Established in the year 1990, with Research & Development as its prime fundamental, Divis Laboratories focuses on developing new processes for the production of Active Pharmaceutical Ingredients (APIs) and intermediates. The company in a short matter of time expanded its breadth of operations to provide complete turnkey solutions to the domestic Indian pharmaceutical industry. Divis Laboratories Limited, whose head office is located in Hyderabad, owns two API manufacturing units, one some 60 km from Hyderabad employing approximately 1500 people, the second similar at Vizag in Andhra Pradesh. Both units are involved in the production of Active Pharmaceutical Ingredients and Intermediates for generics,

custom synthesis of API's and advance intermediates for the giants of the pharmaceutical industry.

### **Applications**

There were two processes in particular which have to be carefully monitored and controlled for safety reasons. The first is a batch reaction process in a glass-lined reactor using highly flammable/volatile organic solvents with strong chemically corrosive properties. The second process, solvent recovery by centrifugation, involves flammable vapors which at an oxygen presence of more than 8% could lead to a dangerous explosion. Therefore, in order to minimize oxygen intrusion, inert nitrogen gas is purged into the reactor and centrifuge. Vapors are collected at the vents at

slight vacuum. To ensure safety, effective and reliable monitoring of the oxygen percentage concentration is highly essential in order to be able to control the amount of oxygen that can intrude into the reactor or centrifuge.

### **Problem**

Originally, the customer had been using an oxygen measuring system from one of our competitors. According to Gopal Krishna, the application engineer, and S. Rama Krishna, the general manager of production, it was found that the system performance was affected by moisture content and traces of organic solvents on the sensing element. They required a more confident system.



M 700.

### Customer's expectations

There were four main points which would have to be fulfilled in order to enter a successful partnership:

- Sensors resistant to organic solvent vapors and moisture
- System repeatability
- Minimum maintenance time
- Reasonable cost of ownership

### METTLER TOLEDO solution

Based on experience, the following METTLER TOLEDO inertization control systems were proposed:

- Measuring system in the reactor:  
Oxygen sensor InPro 6800 with Hastelloy C wetted parts, housing InFit 761, and multi-parameter transmitter M 700.
- Measuring system at the centrifuge:  
O<sub>2</sub> sensor InPro 6800 in combination with housing InFit 761 and transmitter O<sub>2</sub> 4100e
- For each of two auxiliary centrifuges:  
O<sub>2</sub> sensor InPro 6800 in combination with housing InFit 761 and multi-parameter transmitter M 700

### Customer satisfaction

The very challenging performance expectations of our customer were fully realized. Therefore, after the first few months of use, it was possible arrive at an overall positive conclusion:

- The sensors are compact, simple and easy to install
- Maintenance effort is clearly reduced
- Proven track record for similar applications
- The measuring systems are accurate and reliable
- The measuring system were appreciated by the customer inspectors

### Orders realized

Initially, Divis Laboratories ordered one O<sub>2</sub> measuring loop for their Centrifuge and another O<sub>2</sub> loop for their reactor in manufacturing units 1. These were installed in

the first quarter of 2007 and are now in full operation with satisfactory performance. Based on the performance of the above system Divis decided to install a further two O<sub>2</sub>-measuring systems with dual-channel M 700 multi-parameter transmitters for two auxiliary centrifuges. In addition, they also placed a purchase order for two loops for their manufacturing unit two at Vizag, and now another six loops for manufacturing unit 1 (4 loops for centrifuges and 2 loops for reactor inertization).

► [www.mt.com/DO](http://www.mt.com/DO)



## New Optical Oxygen Sensors InPro 6880i for Enhanced Performance

**METTLER TOLEDO's innovative optical DO sensors for biopharmaceutical processes are fully steam-sterilizable, and combine accuracy and signal stability with fast response time.**

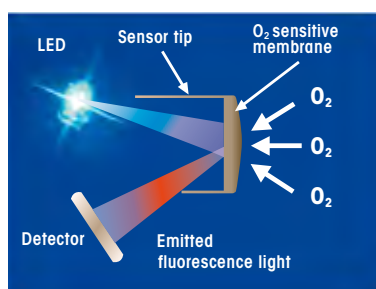
### Optical sensors in the pharmaceutical industry

During fermentation processes, air feed and agitator speed are adjusted on the basis of the measured DO concentration value in order to achieve optimal growth conditions for the microorganisms. Indeed, excessive air feed can even damage the cells, besides leading to wastage of energy by the compressor.

In the pharmaceutical industry mammalian cell culture processes are on the increase. This technology enables the production of highly complex active substances. Mammalian cells react much more sensitively to changes in their environment than do bacterial cultures, and their growth is significantly slower. It is precisely in the case of batch runs of up to 5 weeks that the optical oxygen sensor can here fully demonstrate its inherent strength, namely negligible drift over time. The stable measurement enables batch-to-batch consistency and the maintenance of optimal growth conditions. The new optical oxygen sensor InPro 6880i from METTLER TOLEDO can be used in small, autoclavable research bioreactors as well as in full production-scale vessels.

Compliant to:

- pharmaceutical requirements
- increased process safety
- long maintenance intervals



The identical characteristic in both cases facilitates and accelerates scale-up.

### Measurement principle of the new optical sensors

At the heart of the optical sensor lies the oxygen-sensitive layer which contains immobilized marker molecules. These molecules respond to light by means of a chemo-optical mechanism which is influenced by the amount of oxygen diffusing into the layer. This effect allows determining the oxygen concentration in the sample media.

### Main features of the optical oxygen sensors InPro 6880

The measurement technology of these optical oxygen sensors is designed to meet the most exacting demands. The 12 mm/Pg13.5 sensors are fully sterilizable and autoclavable. They offer reliable measurement accuracy and signal stability, ideal for biopharmaceutical process control. They fulfill the highest pharmaceutical requirements such as N5/Ra16

(Ra 0.4 µm / 16 µm) surface finish, sanitary design, FDA approval, and USP Class VI certified seals.

### Increased process safety

**ISM** Optical technology does not need any electrolyte solution and therefore simplifies handling. The built-in "Intelligent Sensor Management" (ISM®) technology allows for quick startup with "Plug & Measure" functionality and offers advanced diagnostics. The smart digital communication between sensor and transmitter ensures reliability for better process control. ISM helps in deciding whether a sensor is safe for reuse in the next batch or whether it is advisable to carry out maintenance such as membrane replacement.

### Simplified start-up and maintenance ensures availability

The modular sensor design allows disconnecting the sensor shaft from the sensor head, which facilitates autoclaving handling and reduces maintenance effort and costs. The robust O<sub>2</sub> sensitive layer offers increased lifetime and allows fast and easy replacement. Furthermore, the optical oxygen sensor offers maximum availability, since no polarization time is required.

 [www.mt.com/DO](http://www.mt.com/DO)

# Highly Efficient Production Process through Integrated Automation with EasyClean Systems

**At GE Healthcare in Norway, 24 EasyClean Cleaning and Calibration Systems are used in a 3-stage validated process for the production of X-ray contrast media. This has led to reduced maintenance effort and increased efficiency.**

## General Electric Healthcare

GE Healthcare is headquartered in the United Kingdom, and is a \$15 billion unit of the General Electric Company. Worldwide, GE Healthcare employs more than 45,000 people in over 100 countries. GE Healthcare, Lindesnes in Spangereid, Norway, which started up in 1973 with a staff of five, today has about 400 employees. GE Healthcare provides transformational medical technologies and services. Besides many others, GE healthcare has strong expertise in biopharmaceutical manufacturing technologies. Its broad range of products and services enable healthcare providers to better diagnose and treat diseases.

## Contrast media for X-ray treatment

X-ray is the oldest and best known of the medical imaging techniques. High energy radiation is produced in an X-ray tube. If a contrast medium has been injected, blood vessels and specific organs will let through less radiation, resulting in less film exposure. Contrast media are chemical substances, containing chemically bound iodine. Other types of contrast media are based on barium, and are used to highlight the stomach and/or gut, and can either be swallowed or given as an enema.

## The production of contrast media

The iodine-based contrast media produced in this process line are filled into ampules, in China in the form of powders, in the USA as ready-to-use solutions. There are numerous types of iodine-based contrast media. They differ mainly through the type of carrier molecule and “attached” iodine atoms, as well as by their physiochemical properties. Control of the pH value takes on particular significance in the production of contrast media, and it is therefore extremely important that the relevant pH electrodes provide reliable measurement results at all times.

## 3-stage production process

Earlier they took process solution samples, diluted and measured them with portable instruments. In some cases they also had in-line instruments for continuous measurements, but with manual calibration. Tests with retractable housings incorporating a flushing chamber passed off so very successfully, that shortly afterwards the first three cleaning and calibration systems EC 350 from METTLER TOLEDO were installed, each in a measuring loop consisting of:

- pH electrode InPro 4250
- Retractable housing InTrac 777 e
- Transmitter pH 2100 e

This enabled automated calibration and cleaning of the electrodes during the ongoing process. The success of this pH measurement configuration prompted GE

Healthcare, during a recent expansion phase, to equip new production lines with further cleaning and calibration systems of the latest generation from METTLER TOLEDO.

Today, the 3-stage production process presents itself as follows:

### Stage 1

#### Process stage in a non hazardous area

Six large process vessels are each equipped with an EC 350 or with an EC 350 e system.

Stage 1 is carried out in a non-hazardous area. The batches are run simultaneously in parallel.

### Stage 2

#### Process stage in a hazardous area

The intermediate products are transferred to six vessels in a hazardous area.

Whereas the pH measurement systems remain the same, EasyClean EC 400 X is used in this instance.

### Stage 3

#### Process stage in a hazardous area

This final stage was recently put into operation and consists of six vessels situated in a hazardous area. For safety reasons two EC 400 X are installed to each reactor (12 in total). In case one system fails, the second one will takeover the task.

This new section of the plant is equipped with a Profibus network.



EasyClean 400.



M 700.

This enabled each EasyClean system to be fitted with a communication module, which greatly simplified integration into the process control system (Emerson Delta V) and, at the same time, ensured that all advantages of digital communication could be exploited to the full.

### Cleaning and calibration procedure

Either sodium bisulfide or water alone is employed for cleaning purposes. Whilst pH measurement is carried out continuously during the course of the process, electrode cleaning always takes place at the end of each batch. The electrode is retracted from the process into the flushing chamber of

the housing InTrac 777, where it is cleaned, flushed and afterwards parked in the maintenance position until the new batch is ready to begin. At the start of each new batch process, as routine, automatic 2-point calibration of the pH electrode InPro 4250 is effected in both acid and alkaline media.

### Level of automation provides large benefits

Today, the processes are completely integrated in the process control system. The push of a button is sufficient to automatically start off the program for a new batch. Errors through false manipulation are practically ruled out. The data of the automatic calibration of the pH electrode

is reproducible. Maintenance is optimized: the result is minimum servicing at maximum efficiency.

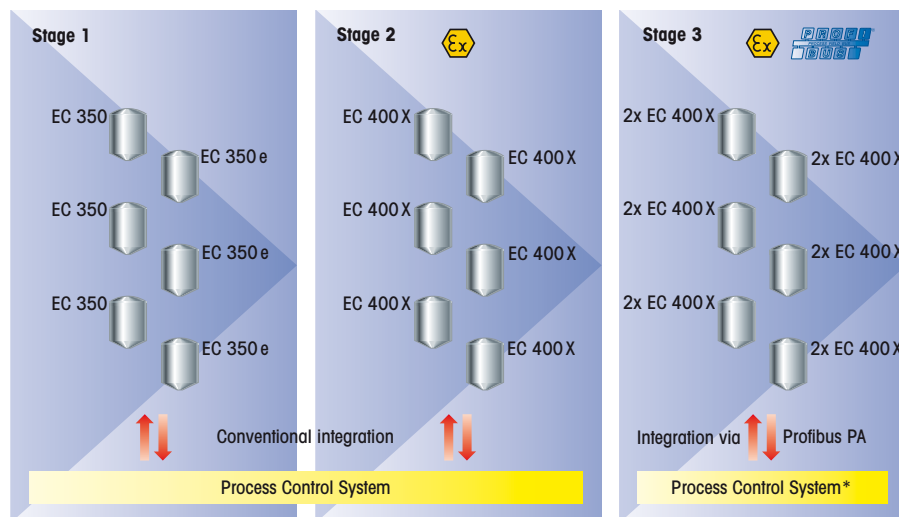
### Importance of process validation

The processes for the production of contrast media have been validated, and received FDA approval. It is imperative to strictly adhere to the approved process, since any alteration whatsoever would make revalidation necessary. In clear text, this means: 2 hours of new programming result in 20 hours of administration effort!

METTLER TOLEDO is represented in Norway by InLine Prossess AS.

► [www.mt.com/easyclean](http://www.mt.com/easyclean)

### Diagram of the production process



EC 350, EC 350 e and EC400 X are today integral components of the 3-stage production process for the manufacture of iodine-based contrast media. These validated processes guarantee the highest level of reproducibility and product quality.

\*Emerson Delta V

# Open Fieldbus Protocols support Asset Management and Plant Maintenance

Open fieldbus technology like HART®, FOUNDATION™ Fieldbus and PROFIBUS® enables the full use of METTLER TOLEDO functional advantages on digital communication:

- improved resolution of measured values,
- intelligent sensor diagnostics and instrument parameter settings
- comfortable instrument configuration out of a central station,
- higher level of process data to improve the plant conditions,
- availability of additional process values to be easily integrated into the control system

Our intelligent analytical instruments are equipped with electronic device descriptions (DD) for various process instrument configuration software tools.

 [www.mt.com/pro-service](http://www.mt.com/pro-service)

## METTLER TOLEDO recommends

- Transmitters for pH/ORP, dissolved oxygen and conductivity

Two transmitter lines for integration in HART®, FOUNDATION™ Fieldbus and PROFIBUS® PA networks.

- EasyClean 400

The cleaning and calibration system EC 400 for an easy integration in FOUNDATION™ Fieldbus and PROFIBUS® PA networks.

- ISM technology

Integration of sensor diagnostic information into the process control environment – “sensor wear monitor” and “adaptive calibration timer” for optimal maintenance planning.



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