Pharmaceutical & Biotechnology

Perspectives in Liquid Process Analytics

22 News

INGOLD

Leading Process Analytics

THORNTON

Leading Pure Water Analytics

Streamline Your Processes with the New iSense Software

Intelligent Sensor Management (ISM®) technology is helping pharmaceutical companies the world over to increase process reliability, reduce sensor lifecycle costs, and simplify regulatory compliance. With the new iSense software for ISM sensors, realizing the benefits of digital sensor technology is easier than ever.

Significant benefits

Analytical measurements are going digital. The advantages offered by the latest, cutting-edge in-line sensors and transmitters, such as greater process quality and yield, reduced sensor maintenance, and simplified regulatory compliance, are hard to ignore.

ISM, METTLER TOLEDO's digital sensor technology, has transformed the way analytical sensors are handled and maintained from first installation to end of life. ISM offers a level of performance and convenience that is not available with other systems.

Convenience is the key

Whether in production or in the lab, the greater the convenience provided by analytical equipment the more efficient will be your processes.

iSense, the accompanying software for ISM, streamlines all your sensor activities. It provides highly valuable features such as sensor calibration away from the process, electronic documentation, instant evaluation of a sensor's "health", and predictive information on when maintenance will be required. The latest version of iSense enables seamless management of ISM sensors and delivers exceptional usability.

It is easier with iSense

Spending hours learning new software is a costly use of operator time, so we have made iSense extremely intuitive to operate.

METTLER TOLEDO

For a new sensor, just connect the Bluetooth® communicator supplied with the software. iSense automatically recognizes the probe and displays a registration page where you can add any important information. The next time that particular sensor is connected, the iMonitor screen will provide an easy-to-read overview of the sensor's condition and, if maintenance is required, tell you what steps to follow.

Whether you want to calibrate a pH sensor, check how a sensor's performance has been affected by a process, or print sensor maintenance documentation iSense guides you through the steps.

For today's processes and tomorrow's

ISM and iSense have been designed to be adaptable to your current needs and your future ones. Planned developments, such as a mobile app that provides a quick sensor check on the go, mean that ISM will remain in the forefront of analytical measurement technologies.

Discover more at:

► **www.mt.com/ISM-pharma**

The smiley provides at-a-glance notification of sensor "health". Diagnostics show that this sensor needs calibrated.

The Sensor History feature allows you to see how a sensor has been affected by process exposure over time and whether it can be safely used for the next batch.

On-screen animations guide you through maintenance procedures, helping to ensure proper handling.

Publisher / Production
Mettler-Toledo AG
Process Analytics
Im Hackacker 15
CH-8902 Urdorf
Switzerland

Illustrations
Mettler-Toledo AG
Okea, Margouillat, Pengyou93, Jgroup I
Dreamstime.com

Flexible, Intuitive, and Intelligent
New Transmitter for All Parameters

Our M800 transmitter series has now been extended. The new M800 1-Channel is a multi-parameter, single-channel device which combines a state-of-the-art user interface and advanced Intelligent Sensor Management (ISM®) technology with the broadest parameter coverage that has ever been available on a METTLER TOLEDO transmitter.

Full parameter coverage

The M800 1-Channel extends METTLER TOLEDO's portfolio of high-performance transmitters with a single-channel instrument that covers all major measurement parameters. pH / ORP, dissolved and gas phase oxygen (amperometric and optical), conductivity, and turbidity measurement are all possible in conjunction with either ISM or analog sensors. The M800 1-Channel's multi-parameter ability means that most applications in process analytic applications, covered until now by different transmitters, can be equipped with just one instrument platform.

Cutting-edge user interface

Transmitters, as the interface between process analytical sensors and the user or control system, are central to successful and efficient production. With its 5.7" full-color, high-resolution touchscreen, simply structured menus, and user management functions, the M800 1-Channel sets a high standard in the market for convenient transmitter operation.

The freely-configurable display provides information on measurement values plus diagnostics data on a single screen. Logbook and user management features offer excellent traceability and operating security. Wizard set-up allows the user to reach any menu in only three touches, reducing training efforts and configuration failures to an absolute minimum.

At-a-glance diagnostics

Thanks to the iMonitor display the condition of each sensor is determined in an instant, allowing preventive action to be taken before processes are affected. The ISM predictive diagnostics tools shown on the iMonitor, such as the Dynamic Lifetime Indicator (DLI), Adaptive Calibration Timer (ACT), and Time to Maintenance (TTM) indicator are color coded and shown in a distinctive way. The sensitivity of the DLI can even be altered to match process conditions.

With the introduction of the M800 1-Channel METTLER TOLEDO offers an outstanding measurement solution for applications across all process industries at a very competitive price.

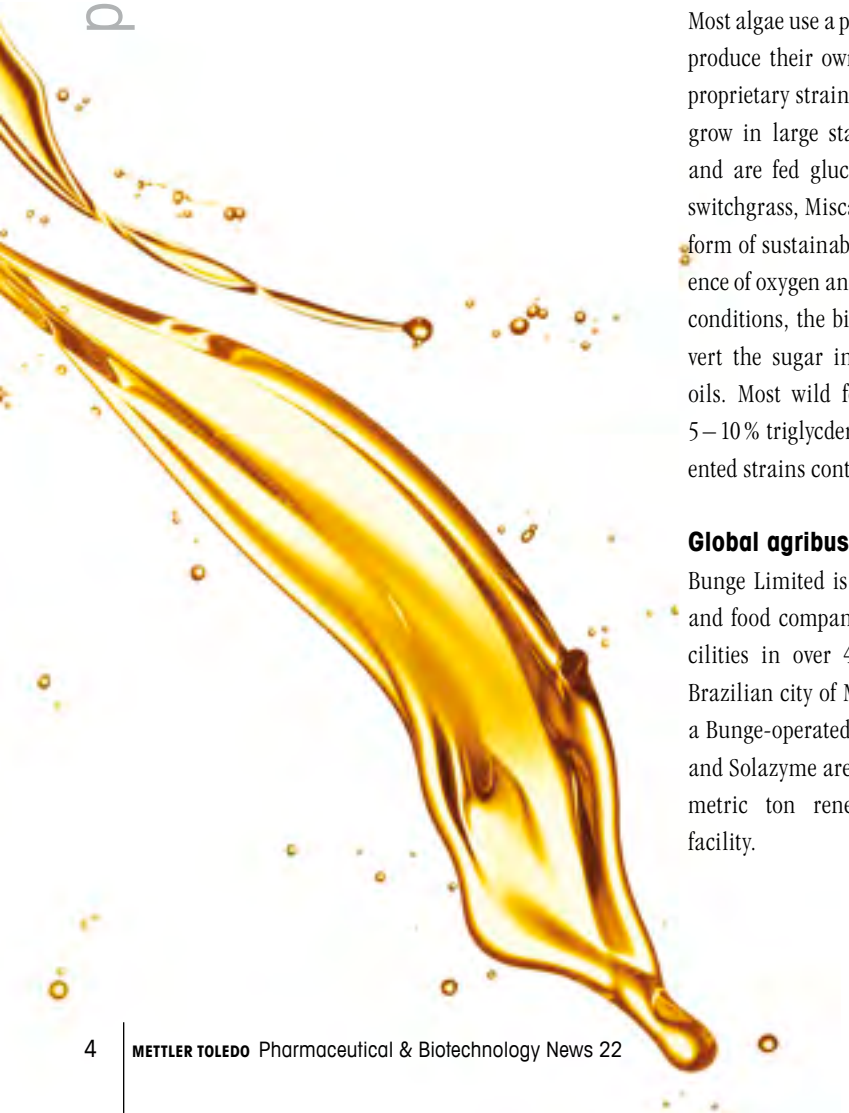
Find out more at:
► **www.mt.com/M800**

From Sugarcane to Oil
with the Help of Intelligent Sensors

Products from the biotechnology industry are being increasingly adopted worldwide. One leading biotech company in a joint-venture with a global agribusiness is constructing a large renewable oil production plant in Brazil. To ensure reliability in fermentation processes they have selected METTLER TOLEDO sensors.

Impressive growth of biotechnology sector

The global biotechnology industry is growing at approximately 11 % per year and by 2015 is expected to be worth US $ 320 billion. This rapid growth is due in no short part to the innovations that biotech companies continue to make in modifying living organisms to develop commercial products.



Renewable oils from algae and glucose

One such company is California-based Solazyme. Since its inception in 2003, Solazyme has used its proprietary biotechnology to produce a wide range of renewable oils for nutritional, cosmetic, chemical, and transportation use; all of them produced from microalgae and plant-based sugars.

Most algae use a photosynthetic process to produce their own nutrients. Solazyme's proprietary strains of heterotrophic algae grow in large stainless steel fermenters and are fed glucose derived from corn, switchgrass, Miscanthus grasses, or other form of sustainable biomass. In the presence of oxygen and in carefully controlled conditions, the bioengineered algae convert the sugar into tailored triglyceride oils. Most wild forms of algae contain 5 – 10 % triglycderide oil. Solazyme's patented strains contain over 80 %.

Global agribusiness

Bunge Limited is a leading agribusiness and food company that operates 400 facilities in over 40 countries. Near the Brazilian city of Moema, and adjacent to a Bunge-operated sugarcane mill, Bunge and Solazyme are constructing a 110,000 metric ton renewable oil production facility.

Innovative use of sugarcane

At the Moema plant it is sugarcane that will provide the energy source for the algae. The cane will pass through the normal first stages of sugar production until pure sucrose juice is obtained. This will be transferred to the fermenters where the genetically-modified algae will feed on the sucrose and rapidly multiply. When maximum biomass is achieved, oil extraction will be carried out through a drying process.

Efficient fermentation requires highly reliable sensors

Achieving maximum yield from the fermentation processes will be dependent on the control of physical and analytical parameters throughout the batch run. As with any other fermentation process, pH and dissolved oxygen (DO) levels will play a critical role, so Solazyme / Bunge want in-line sensors that will provide accurate measurements and operate reliably. They approached METTLER TOLEDO to explore available solutions.

For pH we suggested our InPro 3253 i sensors. This is a low maintenance sensor with high temperature-resistant glass. Its rugged design means it provides fast, accurate measurement even after repeated sterilization cycles.

The InPro 6850 i DO sensor is designed for use in hygienic processes. Its three-electrode measuring principle provides high measurement precision and its easily replaceable membrane and inner bodies reduce service time.

To partner the sensors, we suggested the M400 transmitter. This is a versatile, multi-parameter unit that combines robust construction with easy operation.

Intelligent Sensor Management provides major benefits

It is not just the performance of our sensors and transmitters that attracted Solazyme / Bunge to METTLER TOLEDO. They were drawn to the added benefits that our Intelligent Sensor Management (ISM®) technology brings. ISM simplifies sensor handling and increases measurement reliability, but more importantly to Solazyme / Bunge, it offers predictive sensor diagnostics.

Before starting a fermentation run, Solazyme / Bunge technicians will need assurance that sensors will operate reliably until batch end. With conventional sensors, that knowledge is not available. ISM sensors, on the other hand, continuously monitor their condition and display predictive diagnostics information, such as remaining lifetime or time to maintenance, on the connected transmitter and asset management software. This will allow Solazyme / Bunge technicians to check the condition of sensors before fermentation starts and conduct any corrective maintenance necessary. ISM diagnostics will provide them with a level of measurement assurance that is not possible with analog sensors.

If you want to operate your fermentation processes with confidence, go to:

▶ **www.mt.com/ISM-pharma**

InPro 3253 i pH sensor

InPro 6850 i O_2 sensor

M400 transmitter

Intelligent Sensor Management (ISM®)
for Pharmaceutical Production

ISM is METTLER TOLEDO's digital technology platform for in-line process analytics measurement systems. In production plants around the world ISM is simplifying sensor handling, enhancing measurement integrity, and reducing sensor lifecycle costs.

The benefits of ISM translate into substantial gains for pharmaceutical companies in relation to production process reliability, data transparency, and managing regulatory compliance.

Unlike analog probes, ISM sensors output a robust digital signal, and retain their own calibration as well as process data. Thanks to diagnostics tailored to pharma applications, ISM sensors even predict when they will need maintained or replaced.

In pH, dissolved O_2, dissolved CO_2, conductivity, TOC, and dissolved ozone measurement systems ISM gives you much more than just a measurement.

Greater process reliability

Batch-to-batch consistency
ISM provides accurate information on process conditions, helping to avoid out of spec situations.

Read the white paper on avoiding OOS conditions:
► **www.mt.com/pro-oos**

Easy sensor handling

Convenient lifecycle management
With ISM you can pre-calibrate sensors for error-free exchange at the process.

Watch the video on easy sensor handling:
► **www.mt.com/pro-easy-handling**

Simplified compliance

Full traceability made easy
User-friendly iSense software reduces the workload for meeting regulatory compliance.

Download our guide to water compliance for pharmacopeia requirements:
► **www.mt.com/tho-compliance-guide**

Systems for your processes …
ISM in-line solutions are available for up- and downstream bioprocesses, chemical synthesis, pure water production, clean-in-place/sterilization-in-place systems, and wastewater monitoring.

… adaptable to your requirements
Our ISM transmitter portfolio covers single-parameter, single-channel units for maximum process safety, to multi-parameter, multi-channel devices for greater convenience and flexibility.

Incorporating ISM solutions into your asset management or plant control system via transmitters or converters allows seamless integration of sensor diagnostics information for remote monitoring.

Discover how ISM can help you at:
► **www.mt.com/ISM-pharma**

M800 transmitter showing iMonitor sensor diagnostics utility.

Accurate, Reliable, In-line Measurements

Turbidity System Increases Production Efficiency

During a crystallization process, determining the exact moment of saturation is central to achieving consistent product quality. For a Chinese producer of antibiotics, switching from eye determination to the use of METTLER TOLEDO in-line turbidity systems has improved crystallization efficiency and reduced costs.

Important antibiotic

Ciprofloxacin is a widely used second-generation fluoroquinolone antibiotic used to treat a diverse range of infections. Developed by Bayer HealthCare in 1987, it is now marketed under 300 different brand names worldwide.

One Chinese producer is Zhejiang Guobang Pharmaceutical Co., Ltd. in Zhejiang province. Over 175,000 square meters the company's 10 production areas produce a wide variety of broad-spectrum antibiotics. As the largest supplier of Enrofloxacin in the world, Zhejiang Guobang is well known throughout China for high quality veterinary drug materials.

Exact timing in crystallization process is crucial

Ciprofloxacin production at the facility involves dissolving feed liquid containing impure API in a reactor vessel while gradually increasing the vessel temperature. When the API reaches saturation the medium is then gradually chilled causing pure API to crystalize.

The most critical stage of the process is determining when saturation has been reached. If the temperature rise is halted too soon, API crystal formation will be poor. If stopped too late, causing crystals to form at all can be problematic. Technicians at Zhejiang Guobang were determining by eye when saturation was achieved and this point varied between technicians. This resulted in inconsistent crystallization quality for each batch due to the lack of quantitative standards for the process.

Quantitative solution required

Zhejiang Guobang wanted an in-line turbidity monitoring system that would indicate the precise moment that feeding the reactor and increasing the temperature should be stopped. Xiao Jinfeng, Technical Engineer at Zhejiang Guobang, explains: "For some time we had been searching for a method for quantitative crystallization production which would allow us to achieve automated control. We contacted engineers from METTLER TOLEDO and, after a series of discussions and verifications we chose METTLER TOLEDO turbidity measurement systems."

Greater crystal quality thanks to in-line measurement

The solution installed comprises the InPro 8200 sensor and compatible transmitter. The system uses back-scattered light to detect the level of undissolved particles. Once installed, the first task was to plot the changes in turbidity throughout the saturation process.

InPro 8200 turbidity sensor

- **Improved process control**
  Reliable and reproducible detection of turbidity due to fiber optic technology.
- **Reduced investment costs**
  Suitable from laboratory benchtop level to commercial process installation.
- **Enhanced process safety**
  Freedom from fouling and easy cleanability thanks to uniform, unbroken sensor surface structure.

Xiao Jinfeng noted, "With turbidity detection, we found quantitative indexes which characterize the undissolved state of crystals which had originally been determined by the naked eye. After using the METTLER TOLEDO turbidity meter and statistical data, the crystal color quality on our scale remains higher than the average before the system was installed; the total impurity percentage is reduced from the original average percentage of 0.35 % to 0.3 %; at the same time, impurity peaks are completely removed."

Ease of use leads to quick ramp-up

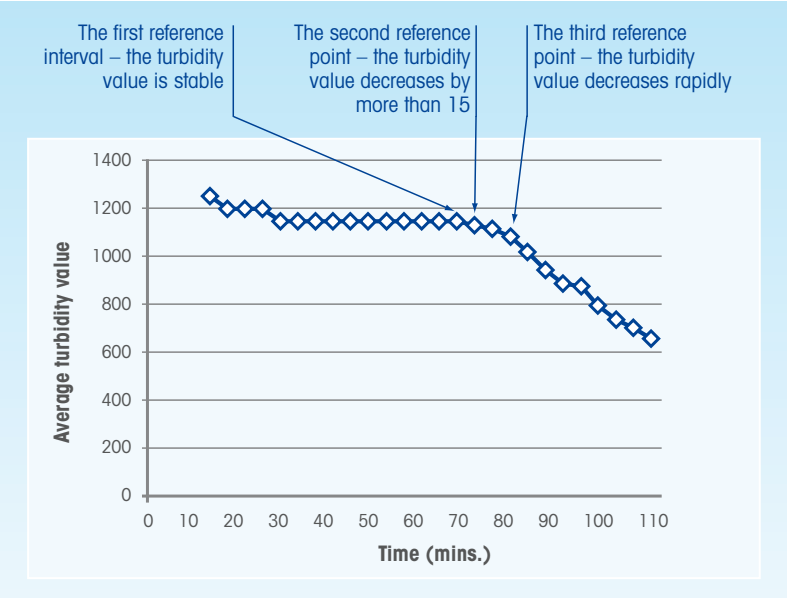
Xiao Jinfeng is also more than satisfied with the METTLER TOLEDO solution's usability, "This system is user-friendly and easy to operate, and has minimum maintenance requirements such as cleaning and calibration. Operators became familiar with the system in very little time."

Faster process at a reduced cost

Of more significance to Zhejiang Guobang, switching to the in-line turbidity system has greatly improved process performance and reduced costs. "According to the statistical data" said Xiao Jinfeng, "crystallization controlled by the in-line turbidity system has largely stabilized the quality of crystal products. At the same time, the reference qualitative indexes have increased the crystallization speed, reduced the temperature rise process by 20 minutes, and saved energy consumption."

If you want to improve crystallization processes at your facility, go to:

► **www.mt.com/turb**



Change in turbidity during saturation process.

Need Quick Profiling of TOC?
Go Portable!

Multiple-point monitoring of Total Organic Carbon can identify contamination sources in water systems. But full system profiling with fixed analyzers can be very costly. The new portable 450TOC analyzer is a convenient and easy to operate solution which can reduce system profiling time by 75 %.

Global regulations are driving TOC monitoring needs

With global regulations limiting levels of organic impurities in pharmaceutical waters used in the manufacturing process, there is an increasing need to monitor water systems at various points for TOC to ensure compliance. Processes such as pure and ultrapure water rinses of production vessels require point of use measurements to ensure water purity and to verify completion of rinsing.

System profiling and point of use measurements

To ensure that water purity complies with regulatory requirements, the most effective solution is to profile the entire water system and monitor water purity at mul-

New portable 450TOC analyzer

tiple points along the system. For the rinsing of production vessels, it is necessary to monitor water purity and also to check the TOC content at the drain until it is verified that the vessel is completely clean.

One of the challenges to achieving a full system profile and monitoring is the capital expenditure required to install fixed TOC analyzers at all the measurement points that should be checked. This has frequently led to facilities measuring at only a few critical points of use along the system and extrapolating that data in hopes of estimating the full system profile. However, this still does not identify specific points of organic ingress or solve the issue of continuously monitoring along multiple points in the system to ensure water purity throughout the process. To do that, a portable system is needed that can monitor quickly at various points in the system to provide immediate measurements.

The portable 450TOC – simple and convenient

The new, portable 450TOC analyzer reduces system profiling time by 75 % and delivers first results 80 % faster than traditional methods. With its portability and rapid TOC measurement technology, the 450TOC analyzer is the perfect choice for quickly profiling water systems or measuring at critical points of use such as at production vessel rinsing.

Key features of the 450TOC include:

- USP 643, 645, EP 2.2.44, Ch P and JP 16 requirements compliance.
- Provides first results 80 % faster than traditional methods.
- Simultaneous data log and print means profiling and troubleshooting can be achieved on the spot as well as at a central data collection and analysis location.
- Rugged design and ease of access to internal assemblies leads to low and easy maintenance.

Find out more at:

▶ **www.mt.com/toc**

USP 1644

New USP Chapter
on Conductivity Measurements

A new general chapter covering the use of electrical conductivity measurement has been made official in the United States Pharmacopeia (USP). Until now, there had never been an official chapter in USP about the proper use of conductivity measurements for general applications. The new chapter, < 1644 > Theory and Practice of Electrical Conductivity Measurements of Solutions, does not replace the USP < 645 > Water Conductivity chapter: instead, it relates to other applications of conductivity measurement in the pharmaceutical and related industries.

USP < 1644 > provides technical guidance in the theory, operation, calibration and maintenance of conductivity measurement systems. Beyond its use in water systems, other conductivity applications include chemical dosing / mixing, fermentation, rinsing, clean-in-place, and resin regeneration.

Content of the chapter includes:

- Benefits / weaknesses associated with on-line process and off-line lab measurements.
- Terms and definitions, along with discussions of the meaning of cell constant, temperature compensation, and various measurement units.
- Key components of a conductivity measurement system – measurement electronics, temperature sensor, cell constant and cables.
- Overview of proper calibration techniques.
- Materials of construction and process connections for on-line sampling.
- Unique considerations for, and benefits of, digital measurement systems.

▶ **www.mt.com/Thornton**

Get in-line with METTLER TOLEDO

Don't leave it to chance!

Heads – I use the sensor again, tails – I don't.

ISM® – True Predictive Diagnostics

No more guessing if a sensor will survive through the next batch. Intelligent Sensor Management's predictive diagnostics analyze process conditions and sensor health to provide you with accurate information on when sensor replacement will be needed.

ISM Intelligent Sensor Management from METTLER TOLEDO

► **www.mt.com/ISM**

Mettler-Toledo AG
Process Analytics
Im Hackacker 15
CH-8902 Urdorf
Switzerland

www.mt.com/pro
Visit for more information