Process Analytical Solutions
Optimizing Pharmaceutical Processes
METTLER TOLEDO
Commitment to Innovation and Quality

METTLER TOLEDO Group

Our company specializes in providing precision instrument equipment and related services to industrial customers. In 2015, METTLER TOLEDO generated revenues of US$ 2.4 billion. The company’s stock has been publicly traded on the New York Stock Exchange since 1997.

Worldwide presence
We have a worldwide distributor network and a workforce of more than 13,500 employees. We support our customers in industry by providing comprehensive solutions for each step of their manufacturing processes – from receipt of materials throughout all manufacturing stages with in-line process measurement, through to final packaging control, logistics and shipping.

METTLER TOLEDO instruments are used in research and development, manufacturing process control and for quality control. The pharmaceutical, biotech, chemical, food and beverage, and cosmetic industries are among the principal users.

Innovation and quality
Our company enjoys an excellent reputation as an innovator demonstrated by R&D expenditures above the average for the industry. We make every effort to achieve the highest level of quality, by applying Total Quality Management at both product and process level, particularly as part of the support we provide to our customers to help them comply with international guidelines.

Process Analytics Division
Within the METTLER TOLEDO Group, the Process Analytics Division concentrates on in-line analytical system solutions for industrial manufacturing processes. The Division consists of two business units, Ingold and Thornton, both internationally recognized leaders in their respective markets and technologies.
InPro®

Thornton is the market leader in ultrapure and pure water analytics, with technology complementing InPro’s process measurement systems.

Thornton Inc, founded in 1963 by Dr. Richard Thornton, a MIT Professor, has been part of the Process Analytics Division since 2001. Thornton’s leading market position is demonstrated by its innovative analytical instruments and sensors for the parameters resistivity, conductivity, TOC, pH, bioburden, dissolved oxygen (DO) and ozone. A new, revolutionary Smart TOC sensor integrated with a multi-parameter transmitter offers unique real-time TOC monitoring in challenging applications within the pharmaceutical and biotech sectors.

Solutions for the Pharmaceutical Industry

Ingold and Thornton solutions contribute to the optimization of production processes, with innovative measurement technology that offers:

- accuracy and reliability
- reproducibility
- traceability
- user-friendliness
- simplified SOPs and validation

The METTLER TOLEDO team of application specialists will assist you in:

- sustaining high product quality
- optimizing yield
- lowering maintenance costs
Production processes and Purified Water quality can be assured through monitoring analytical parameters. For every stage of the manufacture of pharmaceuticals, METTLER TOLEDO in-line measurement systems deliver accurate, real-time evaluation of process conditions.

**High quality, time after time**

It is essential in pharmaceutical operations that process reliability is always high and consistent. In-line measurement and control of pH, conductivity, DO, turbidity and TOC enables reliable, repeatable production of high quality pharmaceutical products.

From the very start of manufacture to the very end, METTLER TOLEDO provides measurement solutions that will make your processes smarter, sharper and more cost-effective.

Our innovative measurement systems offer simple, user friendly operation while assuring consistent monitoring and control with validation capabilities to meet the global regulatory compliance challenges facing system owners.

METTLER TOLEDO offers a broad range of measurement solutions, which allow for integration of our instruments and sensors into both regulated and non-regulated systems. Whether global compliance is required or not, you can be assured METTLER TOLEDO systems are supported by a commitment to provide world-class solutions that bring value, accuracy and measurement integrity for the level of process control required.

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Pharmaceutical waters
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Effluent treatment and scrubbers
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Intelligent Sensor Management (ISM®) is an innovative concept for process analytical measurement solutions. With ISM sensors, maintenance becomes predictable, failure in the process is avoided, and traceability is simple.

**Greater Process Safety**
**And Reduced Maintenance**

**Built-in intelligence**
ISM sensors feature an on-board microprocessor. This brings a number of benefits that non-ISM sensors cannot match; including, stored calibration data and predictive diagnostics.

**Pre-calibration in the lab**
With ISM, buffer solutions do not have to be taken to the measuring point for sensor calibration. Instead, using iSense™ software, sensors can be calibrated conveniently in a lab then stored until they are required. ISM’s Plug and Measure feature means measurement point start up with pre-calibrated sensors is fast and reliable.

**High traceability**
iSense software records the history of all ISM sensor activities such as calibration and maintenance. Complete documentation of ISM sensor assets is available at the touch of a button. iSense CFR features electronic signature and Audit Trail functions and is technically compliant with 21 CFR Part 11 and GMP Annex 11.

**Process safety**
Being able to predict when a sensor is going to fail and therefore prevent its use in the next batch would be extremely useful. This is precisely the function of ISM’s Dynamic Lifetime Indicator (DLI). By constantly monitoring process conditions and sensor “health”, the DLI provides a clear indication of a sensor’s remaining lifetime. For greater accuracy, a sensor can even learn the DLI information from a sensor that has been used previously in a process.

ISM transmitter M800

- iMonitor provides real-time evaluation of sensor condition
- Predictive diagnostics to proactively plan sensor maintenance
iSense

- Verification and calibration of ISM sensors in a convenient location
- Documentation of sensor calibration and maintenance
- Technically compliant with 21 CFR Part 11 and GMP Annex 11

ISM sensors

- Digital sensor-transmitter communication ensures signal transmission stability
- Measurement electronics in the sensor results in higher accuracy
In the manufacture of pharmaceuticals, a fundamental aspect of process quality is the production of Purified Water that meets Pharmacopeia regulations. For continuous assurance of water quality, on-line measurement of TOC, ORP, conductivity and microbial contamination is essential.

Exceeding standards in water purity
When it comes to measuring Purified Water (PW) and Water for Injection (WFI), in-line measurements eliminate the threat of sample contamination, and the need for periodic and costly sampling and off-line laboratory tests.

Pure steam used for sanitization, and WFI are generated from these same waters and must comply with global regulations specifying conductivity and TOC measurements. Validation and verification of analytical measurements with traceable certification, assures regulatory bodies that a system is always in compliance.

Innovative METTLER TOLEDO Thornton systems provide the highest quality and reliability for pharmaceutical and biotechnology facilities where compliance, calibration and validation of pharmaceutical water systems is required.

Flexible, robust and user friendly products simplify installation and use, while providing confidence in performance and reliability.

Bioburden analyzer 7000RMS

- Instant detection and quantification of microorganisms
- Wide measurement range: from 1 cell / 100 mL to 2000 / mL
- Easy operation: no sample preparation, staining or reagents required, touchscreen display
- User-defined alarms and alert threshold
- Low maintenance, sanitizing mode

Wide range conductivity sensors UniCond®

- Certified, pre-calibrated sensors with unique data stored in memory
- Full measurement range in one sanitary sensor
- Withstands high temperature steam and sanitization processes and continuous WFI operation
- ISM technology provides higher accuracy with sensor diagnostics
Total Organic Carbon sensors 5000TOCi and 450TOC

- Continuous, real-time TOC measurement for superior system profiling
- Fast response technology for rapid detection
- Complete process control and precise data trending
- Compliant with all pharmacopeias

Multi-parameter transmitters M300 and M800

- Multi-parameter, single or dual-channel measurement inputs for flexibility and efficiency
- Plug and Measure simplicity with ISM
- ISM technology provides higher accuracy with sensor diagnostics
Maintaining Optimal Conditions During Fermentation

Control of pH and dissolved oxygen is critical to maintaining ideal conditions for the suspended cells and production microorganism. Advanced pH sensor technology keeps the process at the optimal growth rate.

Reliable pH measurement for optimized growth
The sensitivity of enzymatic activities and cellular metabolism to pH changes, necessitates constant pH monitoring and control. The slope and zero point of METTLER TOLEDO electrodes is very stable, even after many sterilization cycles. ISM technology optimizes systematic maintenance management for each individual sensor, which is critical for safe and dependable reuse in the next batch.

Accurate oxygen measurement saves energy
The control of an air compressor by a DO sensor allows significant savings in energy costs by only supplying as much oxygen as needed for the cultures.

METTLER TOLEDO provides polarographic and optical DO sensors with ISM technology for advanced diagnostics. The optical measurement principle offers advantages over polarographic technology such as much lower drift, which is important considering the length of culture fermentations.

CO₂ measurement
Dissolved carbon dioxide levels can be indicative of the quality of cellular metabolism. High partial pressure of CO₂ levels can be an inhibitor to growth and metabolism and may impact product quality characteristics such as glycosylation of proteins.

In fed-batch mode, the dosing of a glucose-containing nutrient can be controlled by a METTLER TOLEDO CO₂ measuring system, maintaining a safe level of CO₂.

Biomass monitoring
The density of biomass is often a key variable, primarily because it provides information on the growth rate and/or product formation. METTLER TOLEDO turbidity sensors provide an alternative to traditional in- or off-line OD measurement techniques which are subject to limitations such as poor linearity. The InPro 8000 series sensors utilize backscattered NIR light to depict true cell mass throughout the entire fermentation.

Optical DO sensor
InPro 6860i

- Optical technology – low maintenance, low drift
- PTFE coated sensing element – easy cleaning, no biofouling
- Versatile output – nA or 4–20 mA or digital ISM via transmitter
**Autoclavable pH electrode**

InPro 3253 i

- Fully autoclavable or sterilizable in situ
- Increased accuracy and stability due to pressurized electrolyte

**Multi-parameter transmitter**

M800

- Multi-parameter and multi-channel
- Color touchscreen simplifies operation
- Plug and Measure simplicity with ISM
Enhanced API Purity
Through Control of Analytical Parameters

Controlling pH and conductivity during ultrafiltration and chromatography allows sharp separation of the desired molecule along with higher purity.

Monitoring of ultrafiltration
Ultrafiltration is often used to increase product concentration prior to high-resolution chromatographic purification. pH and conductivity measurement in the in- and outlet of a UF unit ensure optimal and safe operation. Robust METTLER TOLEDO sensors provide highly repeatable results without compromising accuracy.

Greater efficiency in chromatography
Chromatography and gel filtration are very powerful tools for separation of desired molecules. Conductivity and pH are monitored to check the performance of the pH gradient, the loading of the column, the regeneration, and the reequilibration. Reliability of analytical sensors is central to improving chromatography productivity.

Buffer accuracy improves purification
The pre-pressurized reference electrolyte of the InPro 3250i sensor leads to accurate and reproducible buffer pH adjustment which is key to good separation of molecules.

High performance pH electrode
InPro 3250i

- Very high repeatability
- High accuracy due to pressurized liquid electrolyte
- Easy traceability due to ISM technology
Wide range conductivity sensor
InPro 7100 i

- High resistance against CIP chemicals and sterilization cycles
- WideRange™ technology for measurement from 0.02 to 500 mS/cm

Multi-parameter transmitter
M300

- Multi-parameter, single- or dual-channel
- Plug and Measure feature provides rapid sensor start up
Quality and yield of intermediates and APIs can be greatly improved by high performance in-line process analytics solutions. Reduced chemical consumption is an additional benefit.

**Higher Yield with Less Additives**

**pH/ORP Control in API Synthesis**

Proper pH control improves product purity and contributes significantly to overall cost savings. Securing process availability requires sensors that withstand harsh conditions and the presence of organic solvents, and enable reliable process control.

**Monitoring ORP**
During halogenation, excess bromine has to be reduced following the reaction. The dosing of the reducing agents can easily be controlled by an ORP electrode, avoiding overdosing and preventing the need to take dangerous samples for lab testing. ORP control with METTLER TOLEDO sensors improves the purity of the intermediate and contributes significantly to overall cost savings.

**Top-entry housings**
Glass-lined vessels are the workhorse in API synthesis. For ease of measurement, METTLER TOLEDO housings allow sensor mounting from the top.

**Highly resistant pH electrode**
InPro 4800 i

- Resistant to strong oxidizing media and solvents
- Also measures ORP
- Sensor diagnostics provide continuous monitoring of sensor “health”
Top-entry housings
InFit® 762 e/763 e

- Top-entry housings in PVDF or stainless steel
- Up to 4 m (13.1 ft) insertion length

2-wire Ex transmitter
M400 2HX

- Versatile, 2-wire, loop-powered unit
- Hazardous area approval
- ISM functionality offers advanced sensor management for improved process control
- HART for easy configuration
Optimal Crystal Growth
Through Turbidity Control

In-line turbidity measurement allows optimization of crystallization and leads to improved batch-to-batch consistency.

Turbidity control in crystallizer
By measuring turbidity during crystallization or precipitation processes, the crystal growth rate can be controlled efficiently from cloud point to end point. Real-time turbidity measurement predicts downstream performance and avoids bottlenecks in filtration and drying. Furthermore, the design of seed crystals or the control of the cooling ramp can be triggered by the turbidity signal.

METTLER TOLEDO turbidity measurement systems combine ease of use with flexibility to meet the requirements of a wide range of crystallization applications and increase batch-to-batch consistency.

Optical technology comparison

Single optical fiber, InPro 8100 sensor:
Emitting and back-scattered light travel on same fiber.

Two optical fibers, InPro 8200 sensor:
Emitting and back-scattered light protected by scratch resistant sapphire window.

Single fiber turbidity sensor
InPro 8100

- Single optical fiber
- For high crystal concentrations
- Maintenance free
Dual fiber turbidity sensor
InPro 8200

- Dual optical fiber
- For low crystal concentrations
- Maintenance free

Turbidity transmitter
M800 1-channel

- Color touchscreen simplifies operation
- Available in multi-channel/multi-parameter version
When used as an excipient, the quality levels of Purified Water and Water for Injection must be maintained and therefore continually monitored to comply with global regulations. Verification of water purity is easily achieved with in-line analysis.

Constant monitoring for consistent quality
Because they are always checking, always testing, on-line measurement systems provide instant notification if water quality is out of specification. Therefore, in formulation and filling, real-time conductivity, TOC, bioburden, dissolved ozone and pH measurements are invaluable in helping to maximize yield.

Purified Water and Water for Injection purity levels are defined and regulated by global Pharmacopeia standards which specify unique conductivity, bioburden and TOC limits for each type of water in order to safeguard final product quality. These controls provide assurance to government agencies and consumers that product quality is consistent and within specification throughout the globe. Ozone level control for water system sanitization, and verification of total ozone destruction before Real Time Release of water to production, are essential to water system management and process efficiency.

Highly reliable, low maintenance METTLER TOLEDO Thornton multi-parameter measurement systems provide assurance that pharmaceutical water systems are performing as required and are always in compliance.

Bioburden analyzer 7000RMS
- Instant detection and quantification of microorganisms
- Wide measurement range: from 1 cell / 100 mL to 2000 / mL
- Easy operation: no sample preparation, staining or reagents required, touchscreen display
- User-defined alarms and alert threshold
- Low maintenance, sanitizing mode

Dissolved ozone sensor
- Measures high sanitization levels, and trace amounts to confirm ozone destruct is complete
- Drop-in-place membrane module allows fast and convenient servicing
- ISM technology provides higher accuracy with sensor diagnostics
Safeguarding Purity
Vigilance in Pharmaceutical Water Systems

- Multi-parameter transmitters
  M300 and M800
  - Multi-parameter, single or dual-channel measurement inputs for flexibility and efficiency
  - Plug and Measure simplicity with ISM

- Total Organic Carbon sensors
  5000TOCi and 450TOC
  - Continuous, real-time TOC measurement for superior system profiling
  - Fast response technology for rapid detection
  - Complete process control and precise data trending
  - Compliant with all pharmacopeias
Cleaner, Faster, More Economical
Effluent Treatment and Scrubber Control

Monitoring and controlling analytical parameters results in quicker effluent and waste gas treatment, plus reduced chemical consumption. Automated cleaning and calibration of sensors improves measurement reliability and prolongs their operational life.

Wastewater treatment
In-line analytical measurement systems are invaluable in providing assurance that treated waste meets regulatory requirements. In addition, they can help process waste more efficiently and cost-effectively. Low-maintenance sensors that resist fouling are required in such applications.

Improved scrubber operations
Control of pH or conductivity is very effective in optimizing scrubber performance and reducing chemical consumption. METTLER TOLEDO inductive conductivity sensors withstand scrubber environments – no matter how harsh.

Automatic sensor maintenance
METTLER TOLEDO offers efficient cleaning/calibration systems for pH, dissolved oxygen and suspended solids sensors. Automatic sensor maintenance relieves the burden on maintenance personnel and reduces operating costs.

Open reference junction
There is no diaphragm on the InPro 4260i pH electrode. Instead, an open junction provides direct contact between the measuring solution and the electrode’s solid electrolyte. This minimizes the risk of clogging and the need for frequent cleaning.

Open junction pH electrode
InPro 4260i

- Solid polymer electrolyte for precise measurement and long lifetime
- Open junction eliminates clogging
Retractable housings
InTrac 777 e/770

- Manual or automatic sensor extraction allows maintenance, calibration or replacement without process interruption
- Tri-Lock™ system prevents escape of media

Automatic cleaning and calibration system
EasyClean™ 400

- Ensures maximum sensor performance and availability
- Certified for hazardous area use
Service Offerings Covering our Products
for End Users and Project Engineers at EPCs

METTLER TOLEDO Service
METTLER TOLEDO offers complete services from product consultation to installation and service contracts.

Our comprehensive sales consulting and high level technical services have established us as a competent partner for our customers everywhere around the world. Many global manufacturing companies rely on our competence and our long-standing experience.

Distribution network
Based at several global production sites, with more than 40 market organizations and numerous international sales offices, METTLER TOLEDO maintains a worldwide distribution network and is always close to its customers.

Plant engineering and system integration
Time is money. Our detailed technical product documentation together with local support during specification, installation and commissioning contribute to on-schedule project realization.

Service Offerings
- Repair work at service depot
- Sensor refurbishment
- Installation/commissioning
- Training/seminars/webinars
- Maintenance contracts
- Factory re-calibration
- On-site qualification/verification
- Quality documentation
- Validation support
- Support in compiling SOPs
Asset Management and Plant Maintenance
With HART, FOUNDATION Fieldbus and PROFIBUS

Open fieldbus integration of your process analytical measurement technology into your control system via digital fieldbus technology.

METTLER TOLEDO integration with HART, FOUNDATION fieldbus and PROFIBUS
These open communication protocols are regarded as a standard in the process industry and allow a central overview of the whole plant network. In addition, they offer the opportunity of comfortable instrument configuration and a higher level of process information to improve process performance.

Fieldbus communication with 21CFR Part 11, Asset Management and Predictive Maintenance
By applying HART, FOUNDATION fieldbus or PROFIBUS your efforts to comply with FDA requirements 21 CFR Part 11 will be minimized. The use of Asset Management and Predictive Maintenance is an important issue for improvements in plant management.
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