Pharmaceutical Industry

Process Analytical Solutions
Optimizing Pharmaceutical Processes
Our organization specializes in providing precision instrument equipment and related services to industrial customers. In 2010, METTLER TOLEDO generated revenues of US$ 2 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 11,000 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.
Ingold – Leading Process Analytics

Ingold has a long track record for innovative high-quality solutions for demanding process analytics applications.

Ingold was founded in 1948 by Dr. Werner Ingold. Today, Ingold provides the broadest available range of in-line analytical measurement solutions for industrial processes in the biotechnology, pharmaceutical, chemical and beverage industries. Ingold offers systems for the measurement parameters pH/ORP, dissolved oxygen (DO), dissolved CO₂, conductivity and turbidity. One of the latest developments involves intelligent in-line sensor management solutions for optimized maintenance management in demanding applications.

Thornton – Leading Pure Water Analytics

Thornton is the market leader in ultrapure and pure water analytics, with technology complementing Ingold’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, dissolved oxygen (DO) and ozone. A new, revolutionary Smart TOC sensor integrated with a multi-parameter transmitter is highly successful 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
Intelligent Sensor Management (ISM®) is an innovative new 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

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.

**Built-in Intelligence**

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 Asset Suite 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 or maintenance. Complete documentation of ISM sensor assets is available at a touch of a button.

**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.

- **M800 transmitter**
  - iMonitor provides real-time evaluation of sensor condition
iSense Asset Suite
- Verification and calibration of ISM sensors in a convenient location
- Documentation of sensor calibration and maintenance

ISM sensors
- Digital sensor-transmitter communication ensures higher signal transmission stability
- Measurement electronics in the sensor results in higher accuracy
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, TOC enables reliable, repeatable production of high quality pharmaceutical products. From the very start of manufacturing, 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 has 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.

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.

From Raw Material to Final Products
Your Assurance of Process Reliability

Biopharma
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 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.

Our measurement systems are supported by a commitment to provide best-in-class solutions that bring value, accuracy and measurement integrity for the level of process control required.

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The Starting Point
Confidence in Water Quality

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 and conductivity is essential.

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UniCond® conductivity sensor
• 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

5000TOCe Total Organic Carbon sensor
• Continuous, real-time TOC detection which meets global Pharmacopeia regulations
• Reliable on-line TOC validation
M300 & M800 transmitters

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

Control of pH and dissolved oxygen is critical to maintaining ideal conditions for the suspended cells and production microorganism. More accurate 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 a 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 level 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 the protein product.

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.

InPro 6860 i O₂ sensor
• Optical technology – low maintenance, low drift
• Slim design allows easy mounting in benchtop bioreactors
• Versatile output – nA or 4–20mA or digital ISM
M800 transmitter
• Multi-parameter and multi-channel
• Color touchscreen simplifies operation

InPro 3253 pH electrode
• Fully autoclavable or sterilizable in situ
• Increased accuracy and stability due to pressurized electrolyte
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.

InPro 3250 pH electrode
- Very high repeatability
- High accuracy due to pressurized liquid electrolyte
- Easy traceability due to ISM technology
M300 transmitter
• Multi-parameter, single- or dual-channel
• Plug and Measure feature provides rapid sensor start up

InPro 7100 conductivity sensor
• High resistance against CIP chemicals and sterilization cycles
• WideRange technology for measurement from 0.02 to 500 mS/cm
Securing Quality and Controlling Consumption of Additives
Monitoring pH/ORP in Chemical Reactors

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.

**pH control**
Proper pH control improves product purity and contributes significantly to overall cost savings. Securing process availability requires sensors that withstand harsh conditions, 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.

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**InPro 4800 i pH electrode**
- Resistant to strong oxidizing media and solvents
- Also measures ORP
- Sensor diagnostics provide continuous monitoring of sensor “health”
**InFit® 762 e/763 e housings**
- Top-entry housings in PVDF or stainless steel
- Up to 4 m (13.1 ft) insertion length

**M420 transmitter**
- Versatile, 2-wire, loop-powered unit
- Hazardous area approval
- ISM functionality offers advanced sensor management for improved process control
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

<table>
<thead>
<tr>
<th>Single optical fiber, InPro 8100 sensor:</th>
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<tr>
<td>Emitted and back-scattered light travel on same fiber.</td>
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<th>Two optical fibers InPro 8200 sensor:</th>
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<tr>
<td>Emitted and back-scattered light protected by scratch resistant sapphire window.</td>
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InPro 8100 turbidity sensor

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

Trb 8300 transmitter
- Range of control functions for seed crystal dosing and detection of end point
- Three independent parameter sets for measuring in different media
Safeguarding Purity
Vigilance in Pharmaceutical Water Systems

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, 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 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.

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

5000TOC e Total Organic Carbon sensor
• Continuous, real-time TOC detection which meets global Pharmacopeia regulations
• Reliable on-line TOC validation
M300 & M800 transmitters

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

InPro 4260 pH electrode
• Solid polymer electrolyte for precise measurement and long lifetime
• Open junction eliminates clogging
InTrac® 777 e/770 housings
• Manual or automatic sensor extraction allows maintenance, calibration or replacement without process interruption
• Tri-Lock system prevents escape of measuring media

EasyClean 400 automatic sensor cleaning and calibration system
• 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 embraces the complete range of service offerings provided by METTLER TOLEDO. We offer an attractive range of services to customers, from product guidance, over installation through to service contracts.

**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

**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.
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 the 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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