Pharmaceutical & Biotechnology
Perspectives in Liquid Process Analytics

23 News

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High API Quality, Low Maintenance at Teva Pharmaceuticals

Product quality is of paramount importance to Teva Pharmaceuticals. So, when its Czech subsidiary required in-line pH measurement for API production, it turned to METTLER TOLEDO. Now, API quality is higher plus the pH system looks after itself.

Biggest producer of generics

With an annual production of 73 billion tablets and capsules from over 70 manufacturing sites, Israel's Teva Pharmaceuticals Industries Ltd. is one of the top ten pharmaceutical companies in the world and is the largest manufacturer of generic pharmaceuticals. Teva Pharmaceuticals CR, s.r.o., is a subsidiary of Teva in the Czech Republic. Its plant in Galena produces a wide range of final products but the main focus is on API production.

Lab measurements are not timely

In one of the API production lines acid is gradually added to an alkaline API solution in order to precipitate API crystals from the liquid. Grab samples and lab measurements were being used to determine when sufficient acid had been dosed. This method was time-consuming for personnel and Teva decided to acquire an in-line system that would allow automatic control of acid dosing and which would be simple to maintain.

Advanced in-line solution

The nature of the API production process posed a few issues for in-line pH measurement. Firstly, the large glass-lined reaction vessels cannot support side-entry installation of pH sensors and due to the height of the vessels, top-entry would be problematic. Secondly, precipitation of the API during the process would quickly coat an in-line sensor, necessitating regular cleaning.

METTLER TOLEDO proposed a measurement solution that would not only operate

METTLER TOLEDO

reliably in the conditions, but would also allow Teva technicians to monitor sensor "health" so that any sensor issues could be rectified before measurements were affected.

Robust sensor

InPro 3100 i UD is a pH sensor specifically designed for pharmaceutical use. The "UD" suffix means that the InPro 3100 i can operate upside-down and therefore can be installed in the underside of process vessels.

Modular transmitter

The M700 is a multi-parameter, two-channel transmitter. Three module slots allow it to be configured with two measurement parameters plus a choice of communications protocol. It can also control the EasyClean 400 system mentioned below.

Automatic sensor cleaning system

EasyClean 400 provides fully automatic pH sensor cleaning and calibration. It offers multiple control possibilities and can be extensively programmed for a broad range of application conditions and user requirements. In combination with the M700 transmitter and InTrac 777 e housing, it provides a highly flexible system for use with batch or continuous measurements.

Retractable housing

The InTrac 777 e housing features an internal flushing chamber for sensor cleaning without interrupting the process. The Tri-Lock™ safety system prevents escape of process and cleaning fluids, even when installed upside-down.

Increased uptime

The InPro 3100 i UD and M700 transmitter feature METTLER TOLEDO's Intelligent Sensor Management (ISM®) technology. ISM simplifies sensor handling, enhances process integrity, and reduces sensor life-cycle costs. Plug and Measure ensures fast, error-free system start up, and predictive sensor diagnostics provide real-time data on sensor condition. This allows proactive maintenance leading to greater measurement point uptime.

Consistent quality and minimal maintenance

The complete METTLER TOLEDO solution has made a significant difference to Teva's process: API quality is consistently high, sensor cleaning and calibration are conducted automatically, and when ISM indicates sensor replacement is required, thanks to Plug and Measure it is a quick and simple procedure. Teva now has plans to install similar systems elsewhere in its Galena facility.

Discover more at:

► **www.mt.com/ISM-pharma23**

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Now for All Major Bus Networks
the M400 Transmitter

By enabling real-time monitoring of sensor assets, fieldbus networks can add long-term value to production facilities. With the M400 series of multi-parameter transmitters, advanced sensor diagnostics information is available over HART®, FOUNDATION fieldbus™ and now PROFIBUS® PA; helping to improve process reliability and safety, and lowering operating costs.

Fieldbuses are prolific

The adoption of fieldbuses in the world of automation continues to grow rapidly across all process industries. It is a very well accepted technology and is installed by all major manufacturers worldwide.

Benefits including reduced wiring and installation costs are obvious. Less apparent are the long-term advantages of fieldbus networks that become clear many months after a facility has been commissioned. According to research by the ARC Advisory Group, the greatest benefits of fieldbus networks are realized in relation to maintenance and operation. This means fieldbuses themselves are often not a lasting cost-saver directly, but merely allow a higher level of asset management that can significantly reduce operating costs.

As an example, a fieldbus can simplify the collection of device data for Plant Asset Management systems that track the condition of the connected field devices and sensors. METTLER TOLEDO, as a manufacturer of intelligent sensors and transmitters, rose to the challenge of providing real-time information on the installed sensor base.

Remote diagnostics avoid needless maintenance trips

We fulfill this requirement with our unique Intelligent Sensor Management (ISM®) technology. Contrary to conventional analog sensors, digital ISM sensors offer flexible integration of key diagnostics data into control systems for remote monitoring. Besides the transmission of the process variables via common communication protocols, sensor identification as well as the diagnostics can be directly accessed via control systems or standard asset management tools. Due to this direct access to information on fieldbus instruments, unnecessary trips to the field can be avoided.

M400 – a common platform for all applications

Our successful M400 transmitter series exemplifies our commitment to continuous improvement in order to meet customer requirements, especially in the area of digital communication.

The M400 is already available with HART and FOUNDATION fieldbus communication protocols. Now, we have completed the portfolio with the introduction of our PROFIBUS PA version.

Across all process industries the M400 provides excellent reliability and reduced total cost of ownership by offering diagnostic utilities and a wide range of communication capabilities.

Find out more at:
▶ **www.mt.com/M400**

ISM®
HART COMMUNICATION PROTOCOL
Fieldbus Foundation
PROFIBUS

Highlights of the M400 PA

- PROFIBUS PA communication
- Covers wide range of parameters including (optical) dissolved oxygen
- Multi-parameter capability reduces inventory
- Mixed mode for easy transition from analog to ISM technology
- Available approvals for hazardous area use: NEPSI, ATEX/IECEx Zone 1

95 % Drop in Manufacturing Deviations
Thanks to Optical DO Measurement

A major biotechnology company was experiencing variations in product quality associated with dissolved oxygen levels. These were due to incorrect measurements from polarographic sensors. Switching to intelligent sensors with optical technology has eliminated almost all of these aberrations.

DO measurement at major biotech facility

A global leader in biotechnology operates a large facility in California. Here, over 40 bioreactors from seed train to 15,000 L are used for mammalian cell culturing.

Maintaining ideal oxygen levels in the reactors to ensure high productivity is an essential requirement, and for this, production technicians at the plant were using a competitor's polarographic dissolved oxygen (DO) sensors.

The cost of erroneous readings

Lab measurements showed that the sensors were reporting inaccurate results on almost every batch run. These false data were resulting in manufacturing deviations and wasting considerable man hours in rectifying sensor problems. In addition, the sensors were being returned to the manufacturer for service after each run, at considerable expense.

High-performance optical measurement technology

After consulting with local METTLER TOLEDO engineers, technicians at the facility evaluated our optical DO sensor InPro 6860 i. This sensor, designed specifically for the biopharmaceutical industry, offers a number of advantages over polarographic sensors. The InPro 6860 i is extremely stable, even over long batch runs. This is due to the optical measurement technology it utilizes and its Automatic Stability Control feature. And unlike polarographic DO sensors, the InPro 6860 i requires no polarization before use.

In addition, the maintenance requirement for the sensor is very low. Only one component, the OptoCap oxygen-sensing element, requires periodic exchange which only takes a minute to complete.

M400 transmitter

InPro 6860 i optical dissolved oxygen sensor

One-piece OptoCap exchange

Transmitter for asset management systems

The transmitter we suggested for this system is the M400 FF 2-wire. Because of the implemented standardized FOUNDATION fieldbus™ interface, the M400 FF supports corresponding asset management tools such as AMS (Emerson) and PRM (Yokogawa), and field communication tools including HH 475. This ensures maximum compatibility with asset management systems. It was particularly suitable for our customer as it would integrate easily with their existing Delta V platform.

Fast start up and real-time diagnostics

Intelligent Sensor Management (ISM®) technology incorporated in the system provides sensor verification and pre-batch diagnostics in the lab using the iSense software tool, error-free Plug and Measure start up, and real-time sensor diagnostics available on the M400 FF and over FOUNDATION fieldbus.

iSense software tool

iSense provides sensor calibration away from the process, electronic documentation, instant evaluation of a sensor's "health", and predictive information on when maintenance will be required.

Huge reduction in manufacturing deviations

Satisfied that the METTLER TOLEDO solution would meet its requirements, 45 such systems were installed at our customer's facility. Since installation, technicians at the plant report that manufacturing deviations associated with DO measurement have reduced by 95 %. Further, our customer says that operator time spent on sensor maintenance is considerably lower.

Find out how your facility can benefit from optical DO measurement at:

▶ **www.mt.com/InPro6860i**

High Confidence in WFI Quality
for a Leading Supplier of Pharmaceutical Seals

To ensure cleanliness of seals and enclosures for pharmaceutical use, they are rinsed in Water for Injection. Technicians at Datwyler Group's Italian production facility became frustrated with the unreliable performance of their total organic carbon instrument which was causing uncertainty over WFI quality. Their search for a dependable measurement led them to METTLER TOLEDO Thornton's 5000TOCi. Now, TOC measurement is accurate and fast.

Global supplier of sealing products

Switzerland's Datwyler Group is a leading producer of sealing solutions for a wide variety of industries. They are the world's second largest supplier of rubber and aluminum closures for pharmaceutical use. In the company's Pharma Packaging facility near Milan, Italy, Datwyler manufactures rubber parenteral components for sealing glass vials and flasks.

WFI must always be within spec

To ensure their finished products are exceptionally clean, the seals are washed with WFI. Facility technicians need to be confident that the water from the WFI system is always within specification. Total organic carbon (TOC) is a vital indicator of water purity, and to be considered WFI its level must be no higher than 0.5 mg C / L.

Datwyler were using an on-line TOC instrument to monitor WFI quality and regularly noticed that TOC levels were higher than permissible. However, lab measurements always indicated that TOC was below the threshold value. Further investigations revealed that trace substances, not detrimental to the WFI, were causing the on-line sensor to report inaccurate readings.

On-line beats lab measurements

Datwyler strongly prefer on-line measurements to those from the lab as they minimize the risk of contamination and provide real-time data, allowing any required corrective action to be conducted quickly. Because the existing system was consistently reporting erroneously high TOC levels, technicians could never be certain of the WFI quality without conducting lab measurements. As a result, facility managers began looking for a new solution. They were resolute in finding a sensor that would not only be dependable, but would also provide rapid TOC analysis and be easy to maintain.

Immune to trace contaminants

METTLER TOLEDO Thornton introduced them to our 5000TOCi Sensor. This device accurately determines TOC by first measuring the conductivity of the sample water. Next, the sample passes through a glass coil where it is exposed to ultraviolet light which breaks down any organic material in the sample. This causes an increase in the sample's conductivity which is then measured by a second conductivity sensor. The difference between the two conductivity readings correlates to the TOC level in the WFI.

We provided a 5000TOCi for Datwyler to test. Within a month, facility technicians were confident in the sensor's ability to measure TOC quickly and accurately without being affected by the trace substances in the WFI. However, reliability was not the only aspect of the sensor that impressed them.

Predictive diagnostics for proactive maintenance

The 5000TOCi features METTLER TOLEDO's Intelligent Sensor Management (ISM®) technology. ISM is an innovative concept for process analytical measurement solutions that simplifies sensor handling, enhances process integrity, and reduces sensor lifecycle costs. ISM features in the 5000TOCi include advanced diagnostics that predict when maintenance will be required. Advance notice of maintenance means that it can be scheduled for a suitable time rather than having to take the sensor off-line after a failure has already occurred. In addition, the sensor stores up to four calibration and system suitability test (SST) reports, further simplifying maintenance.

No more lab testing

A 5000TOCi was purchased and installed and is now providing Datwyler with a level of confidence in their TOC measurements that they never had before. So much so, they no longer conduct lab measurements.

If you need continuous and reliable TOC measurements, go to:

► **www.mt.com/toc**

Highlights of the 5000TOCi Sensor

- Meets USP <643>, <645>, EP 2.2.44, Ch P and JP 16 requirements for the pharmaceutical industry
- Drastically reduces record keeping through simplified data collection with innovative Peak and Average TOC measurements
- Improves the quality and reliability of calibration and System Suitability Testing (SST)
- Interfaces with the M800 multi-parameter analyzer/transmitter

Safe and Simple Weighing
in API Repackaging Areas

ACEF has invested in six new Active Pharmaceutical Ingredient (API) dispensing units, each incorporating an Excellence Balance. Its Quality Assurance Manager, Carlotta Bormioli, explains how METTLER TOLEDO's weighing solutions ensure operator safety and integrate into ACEF's quality control system.

Invest for highest quality requirement

ACEF, located in Fiorenzuola d'Arda, Italy, specializes in the repackaging of chemical and pharmaceutical raw materials, and is a market leader in the distribution of cosmetics ingredients, excipients, APIs and food additives. Their particular expertise lies in the flexible and safe repackaging of materials under strict quality control procedures. Incoming raw materials are inspected and analyzed before being repackaged, labeled and having a certificate of analysis issued. ACEF has recently invested in six down-flow dispensing areas, incorporating six new Excellence Balances, for API repackaging in order to comply with the highest GMP quality standards.

Simple and traceable weighing

ACEF had the following requirements for the improvement of their balance operation and general weighing processes:

- Avoidance of cross contamination
- Short settling time
- Simple weighing procedure for operators
- GMP compliant documentation
- Reliable routine testing and maintenance

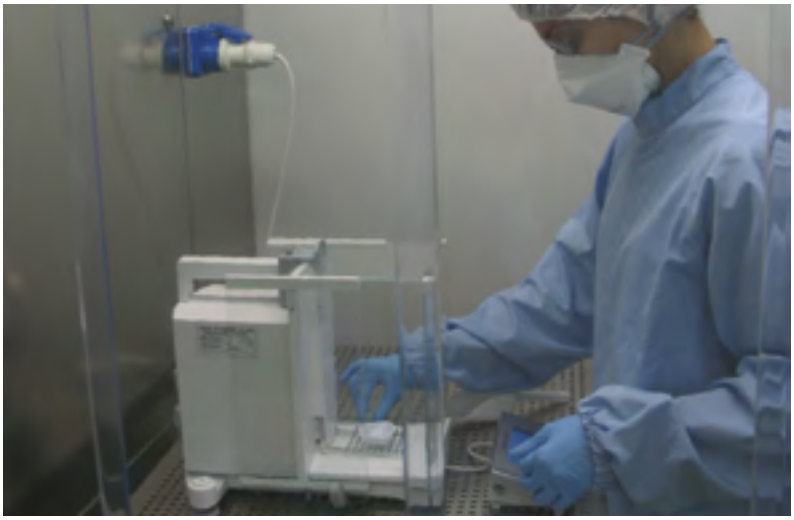
Following the careful analysis of process requirements through METTLER TOLEDO's GWPBase™ recommendation tool, ACEF selected three XS6001S Precision Balances for weighing packages between 100 g and 5 kg, and three XS204 Analytical Balances for packages between 5 g and 100 g.

Solutions that surpass requirements

Carlotta Bormioli was very impressed at how the balance selection process took into account ACEF's specific Quality System requirements. She appreciated the easy cleaning concept of the XS204 Analytical Balance and decided that it was the correct balance for them. The draft shield can be fully dismantled in seconds and cleaned in a dishwasher. The weighing procedure ensures that no balance part is in direct contact with the sample reducing the cleaning validation to a cleaning verification.

Despite the unfavorable weighing conditions caused by down-flow, the XS204 Analytical Balance's SmartGrid weighing

ACEF, Fiorenzuola d'Arda plant, Italy



Katiuscia Ferdenzi operates the XS204 Analytical Balance in the down-flow dispensing area.

XS6001S Precision Balance in down-flow dispensing area.

pan contributes to short stabilization time and the XS6001S Precision Balance, with the larger weighing platform, performs excellently.

Carlotta Bormioli appreciates all the additional features offered, including the standardized touchscreen user interface, which simplifies user operation. Bluetooth printers are located outside the dispensing areas in order to avoid paper contamination and meet the documentation requirements according to GMP. XS Balances are future-proof and support paperless documentation thanks to Ethernet connectivity and One Click™ data management solutions.

Finally, METTLER TOLEDO provided ACEF with CarePac® Routine Testing Weights and maintenance contracts in accordance with the GWP® recommendation to complete all requirements.

- **www.mt.com/XS-analytical**
- **www.mt.com/XS-precision**

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. And the new mobile app provides a quick sensor check on the go.

In pH, dissolved O_2, dissolved CO_2, conductivity, TOC, and dissolved ozone 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**

Free guide: Achieving Greater Process Reliability with Intelligent Sensor Management

This free guide includes best practice examples from leading pharmaceutical companies:

- Greater Process Integrity with Intelligent Sensors
- Getting to PAT with Process Analytical Equipment
- Convenient Conductivity Calibration to Meet Pharmacopeia Regulations

► **www.mt.com/ISM-reliability-guide**

All-Encompassing Solution
for Moisture Control in Tablets

A German pharmaceutical company took advantage of an opportunity to trial METTLER TOLEDO's new moisture analysis solutions. The new HX204 Halogen Moisture Analyzer with innovative features, such as personalized shortcuts and real-time drying curves, and SmartCal, the innovative reference substance for verifying instrument performance, were put to the test and announced as a success after just a few days of testing.

Meet pharmaceutical quality requirements with the new HX204.

The quality team that undertook the trial of these new solutions was responsible for moisture control prior to tablet pressing. They were interested in trialing the new solutions with a view to optimizing processes in their quality lab. The combination of the new HX204 Moisture Analyzer and SmartCal not only provided them with a full solution for ensuring accurate and reliable results, but also made moisture analysis easier than ever before.

Easy result tracking

The team particularly liked being able to follow the drying process of each sample in real-time on the screen and appreciated being able to recall the recorded drying curves later on or transfering them to external data carriers. For frequently analyzed products, the team was able to define control limits so that a green or red results screen indicated pass / fail measurements at a glance. The integrated control charts plotted the moisture content trend for each product over time enabling the team to provide a faster optimization of tableting processes in their production department.

Solid compliance

New features, such as automatic balance adjustment and level control, ensure that the instrument is producing consistently accurate results. In addition, the HX204 can be tested at any selected temperature to ensure that it is performing optimally under specific operating conditions (e.g., the typical point of operation). The temperature unit can also be adjusted accordingly.

A particular benefit for the quality team was the new intuitive graphical user interface with customizable home screen and integrated workflows which enabled users to start working right away. The home screen was personalized to show only the information each user needed for his daily tasks. Password protection and access rights ensured SOPs were met, and the most frequently used methods were activated directly with shortcuts. All are ideal preconditions to ensure error-free operation.

Instrument verification

The quality manager also liked working with SmartCal. SmartCal is an innovative granular substance containing a defined amount of moisture and used to verify moisture analyzer performance with a simple 10 minute test. The user simply pours SmartCal into the sample pan and starts the test. An instrument is working within specifications if the moisture result falls within the SmartCal control limits. Testing the instrument regularly with SmartCal ensures verified instruments, accurate results and seamless QC documentation. A Certificate of Analysis is

Cleaning has never been so easy.

SmartCal – The reference substance for testing moisture analyzers. The certified SmartCal is recommended for use in all highly regulated industries.

provided for every cSmartCal production batch. The independent German Federal Institute for Materials Research and Testing in Berlin issues this certificate.

Clean in 30 seconds

Last, but not least, the laboratory technicians found the new moisture analyzers much easier to clean. The innovative design of the HX204 features a weighing cell at the rear of the instrument to separate it from the heating unit. There is only the hanging weighing pan inside the measurement chamber, which is now completely flat and sealed. It is no longer possible for spilled samples to contaminate the weighing cell. Any spills can be simply wiped away within seconds.

Text: Claas Boerger,
Product Manager Moisture Analyzer

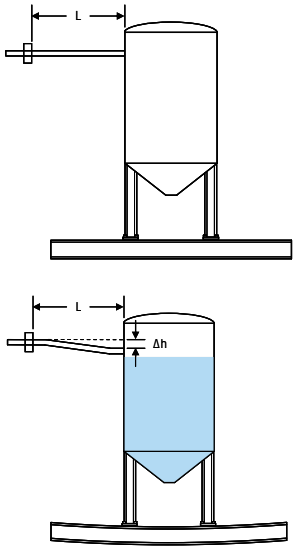
Control charts visualize results and control limits over time.

Personalized home screen for each user.

▶ **www.mt.com/hxhs**

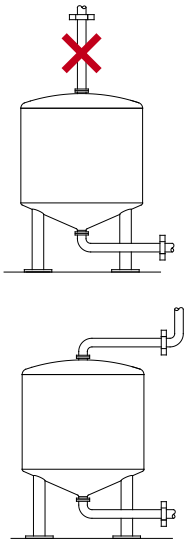
Increase Accuracy
with Correct Piping Connections

Gravimetric level control for tanks is one of the most accurate inventory control methods available. However, piping connections to the tank must be designed to minimize unwanted forces that can cause inaccurate weighing results. Consider the following guidelines when designing a tank weighing system.



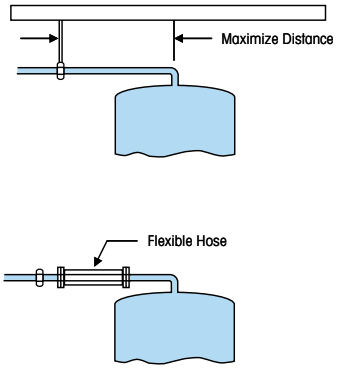
Support structure

A tank scale deflects downwards as load is applied to it. Make sure the tank's support structure deflects as little as possible. That will decrease the amount of deflection in the piping and reduce undesirable vertical forces. Use pipe with the smallest diameter and lightest gauge possible. That will make the piping more flexible.



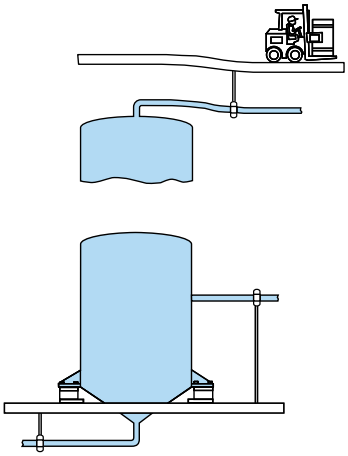
Pipe orientation

Run all pipes horizontally from the tank so that the tank is not suspended by the piping. Pipes may leave the tank vertically or at any angle to the horizontal but must turn and run horizontally before they are supported. Minimize the number of pipes connected to the tank scale by, for example, first connecting them in a manifold with a single horizontal connection to the scale.



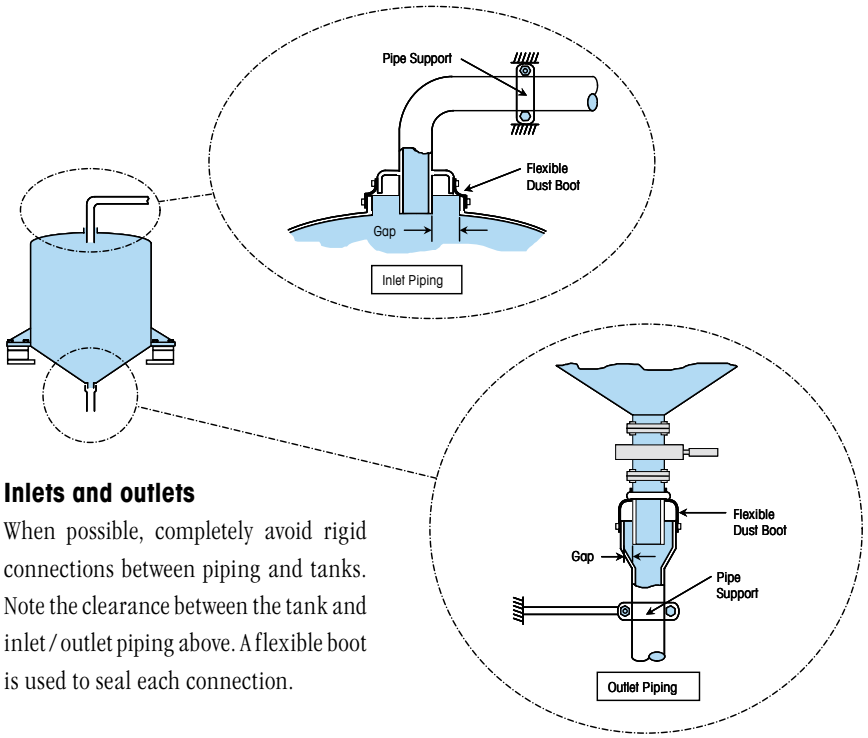
Location of rigid support

Locate the first rigid support for the piping as far away from the tank as possible. That will make the piping more flexible. Use a section of flexible piping or lateral movement expansion joints fitted horizontally as the final connection to the tank scale to further decrease unwanted forces when the tank deflects.



Attachment of support

Do not attach piping to supports for a mezzanine, upper floor, or other structure that deflects independently of the tank. If possible attach piping to the tank's support structure so that the piping moves along with the tank.



Inlets and outlets

When possible, completely avoid rigid connections between piping and tanks. Note the clearance between the tank and inlet / outlet piping above. A flexible boot is used to seal each connection.

Webinar

Learn About Accurate Tank Weighing

► **www.mt.com/webinar-ind-tank-weighing**

Get in-line with METTLER TOLEDO

Ask an Expert
Jim Knows Best

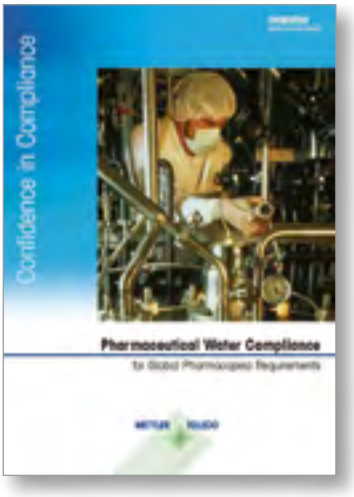
Industry expert Jim Cannon can help you with your questions regarding pharmaceutical waters regulations, applications, and calibration.

► **www.mt.com/jim-knows-best**

Cost Savings Calculator
for pH and DO Systems

Find out how much time and money you can save by switching to Intelligent Sensor Management (ISM®) pH and dissolved oxygen measurement systems.

► **www.mt.com/ISM-pharma-calc**



Complimentary Guide
Water Compliance for Global Pharmacopeia Requirements

In this free guide we review the upcoming requirements of USP <645>, USP <643>, and the acceptable calibration methods and procedures that support the advantages of on-line testing.

► **www.mt.com/tho-compliance-guide**

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

www.mt.com/pro
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