Pharmaceutical Industry Solutions

Reliable Liquid Analysis

ROSEMOUNT® Analytical

EMERSON™ Process Management

A New Standard in Liquid Analysis for Process Control

On-line electrochemical measurements, such as pH, dissolved oxygen, conductivity, chlorine, and ozone, provide substantial improvements in the level of process control, quality, efficiency, and profitability that can be achieved in pharmaceutical bioprocessing.

With so much at stake, it is critical to utilize equipment that has been specifically designed to withstand the challenges inherent in pharmaceutical and biotechnological processing to maximize instrument life, and minimize maintenance while providing accurate and reliable process control. The liquid analysis professionals at Emerson Process Management are ready to put their 60-plus years of experience to work for you. We'll evaluate your application and deliver an optimal, real-world, customized solution for your specific requirements, utilizing world-class Rosemount Analytical sensors and instrumentation.

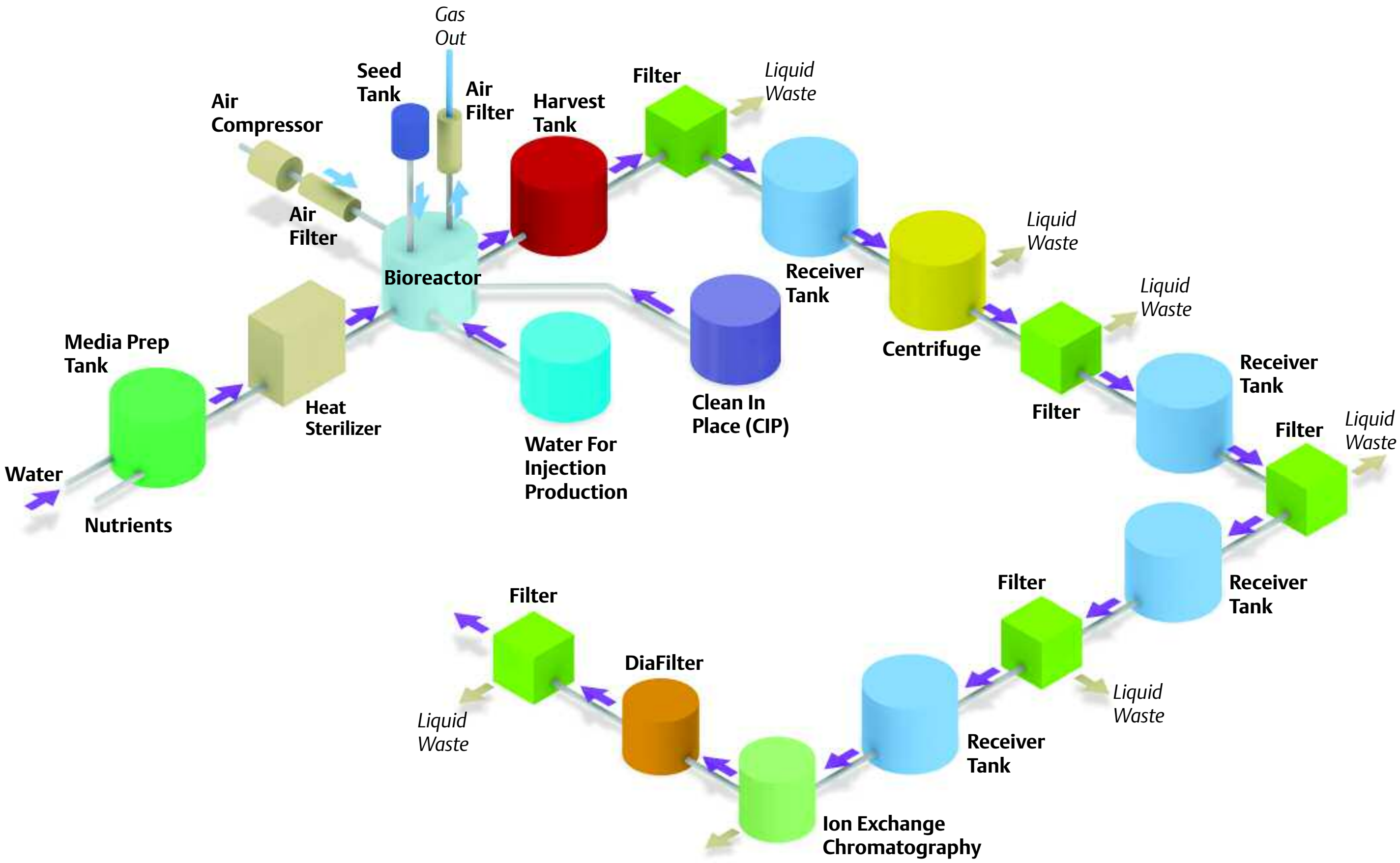
Water is one of the most widely used raw materials in the pharmaceutical and biotechnology industries. Incorporating a properly defined and validated water system will benefit pharmaceutical and biotechnology companies through quality control, and by reducing capital costs, lifetime maintenance costs and monitoring costs.

Several grades of water are used in pharmaceutical plants. Water for Injection (WFI) is one grade that must meet certain federally regulated guidelines set forth by the United States Pharmacopoeia (USP). The entire process must meet sanitary standards. Clean in Place systems ensure that no cross-contamination occurs between batches. Analytical measurements such as pH, dissolved oxygen, and conductivity ensure that the Active Pharmaceutical Ingredient is made within the guideline of current Good Manufacturing Practices (cGMP).

After the batch is completed, the effluent water must be cleaned prior to discharge. Dissolved Oxygen, Chlorine, and pH sensors ensure that the water has been sufficiently cleaned so it can be discharged back to the municipal water districts.

For these applications and more, count on Emerson. Our full line of Rosemount Analytical sensors and measurement solutions for pharmaceutical applications are proven solutions. When you bring your problem to Emerson, consider it solved.

Pharmaceutical Production Overview



The key benefits of process control – quality, efficiency and profitability – can greatly impact all aspects of pharmaceutical bio-processing. These bioprocesses typically include several operations such as production of water for injection (WFI), chemical synthesis, fermentation, cell separation and harvesting, concentration and waste treatment. The nature of the fermentation process and aggressive cleaning regimens, such as steam-in-place (SIP) and clean-in-place (CIP), provides special challenges for electrochemical measurements typically employed throughout the bioprocess cycle.

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Water For Injection

Water is one of the most widely used raw materials in the pharmaceutical and biotechnology industries. Incorporating a properly defined and validated water system will benefit pharmaceutical and biotechnology companies by reducing capital costs, lifetime maintenance and monitoring costs.

The pharmaceutical industry utilizes six grades of water. The most widely used grades — purified water (PW) and water for injection (WFI) — are used for compounding, cleaning, and as ingredients for production of the remaining four grades of water used in making bulk pharmaceutical chemicals (BPC). However, due to the potential for microbial growth introduced through the use of deionization, ultrafiltration (UF), and reverse osmosis systems (RO), these water systems must be properly validated and controlled to ensure water quality specifications are met.

Conductivity is a proven and accepted in-line indication used to ensure water quality of PW and WFI. Conductivity at low levels may be expressed as resistance (MΩ/cm), which is simply the inverse of conductivity R=1/C. The conductivity standard for PW and WFI is less than 1.3 µS/cm at 25°C for in-line measurements. U.S. Pharmacopoeia (USP) recommends that WFI meet purified water requirements.

According to USP, the accuracy of conductivity instruments must be verified and maintained within published USP guidelines. Compliance to USP Stage 1 procedures requires that conductivity measurements be performed without temperature compensation (raw conductivity) and compared with temperature and conductivity values from the appropriate USP data table. Water that does not meet USP Stage 1 conductivity requirements (Figure 1) may still be tested under published Stage 2 and Stage 3 requirements, which must be made off-line with the sample temperature controlled to 25°C. Therefore, it is beneficial to use instrumentation capable of measuring both temperature compensated and uncompensated conductivity simultaneously in order to optimize a plant's process control and validation procedures.

Figure 1. USP 28 Stage 1
Temperature and Conductivity

Temperature (˚C)	Conductivity (µS/cm)	Resistivity (MΩ-cm)
0	0.6	1.67
5	0.8	1.25
10	0.9	1.11
15	1.0	1.0
20	1.1	0.91
25	1.3	0.77
30	1.4	0.71
35	1.5	0.67
40	1.7	0.59
45	1.8	0.56
50	1.9	0.53
55	2.1	4.48
60	2.2	0.45
70	2.4	0.42
75	2.5	0.40
80	2.7	0.37
85	2.7	0.37
90	2.7	0.37
95	2.9	0.34
100	3.0	0.32

Source: USP 28 NF21 (2005)

Temperature compensation for processes greater than 10 µS/cm utilizes linear algorithms to compensate for the changes in temperature. An example of linear temperature compensation is a

>>> *Conductivity is a proven and accepted in-line indication used to ensure water quality.*

Dual Conductivity Instrument, SoluComp II, with Preprogrammed USP Curves to ensure water for injection meets the stringent USP requirements

straight-line correction of 2% of the reading for each 1°C change in temperature. This method works well for general conductivity.

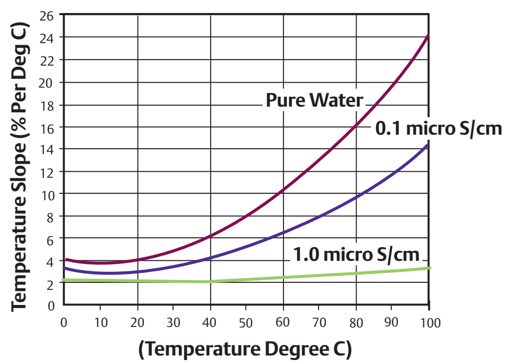
However, water below 1.0 µS/cm requires a different algorithm to properly compensate for the effect of temperature, because as temperature increases the dissociation constant increases, increasing conductivity dramatically. Linear temperature compensation, applied to the high purity range, will result in large errors in measurement. Figure 2 illustrates that measuring the conductivity of 1.0 µS/cm at 85°C will result in an error of about 25%, if linear temperature compensation is applied. For conductivity ranges below 0.1 µS/cm at 85°C, the error can be more than 200%. High purity algorithms are non-linear because they take into account the temperature effect on the dissociation of pure water (non-linear) and the temperature effect on the mobility of the contaminating ions (linear). The magnitude of difference between an uncompensated and compensated conductivity reading at higher temperatures can be large.

Therefore, it is critical to ensure that your selected conductivity instrumentation has the high purity temperature compensation feature.

NIST Traceable Portable Conductivity Validation Kit (including Conductivity Sensor Model 404, Tubing and 1055 Analyzer with Stored USP Values) facilitates the calibration of on-line conductivity sensors

High purity water conductivity measurements can also be very difficult to calibrate and must be performed according to USP guidelines: comparing the cell (sensor) against a National Institute of Standards and Technology (NIST) traceable calibrated cell of a known cell constant or calibrating the cell in a certified solution. However, upon exposure to the atmosphere, high purity conductivity standards and water are easily contaminated by absorption of carbon dioxide from the surrounding air and any residues in the sample container, so extreme care to prevent contamination is required.

Figure 2. Slope for Low Conductivity Water



Therefore, it is recommended to use cells precalibrated to NIST standards available from Emerson in conjunction with a kit, such as the NIST-traceable conductivity validation kit. The portable kit contains a NIST-traceable, flow-through conductivity cell, which can be connected to the process sample point via tubing, eliminating the effects of the atmosphere and providing a reliable, accurate, and validated measurement.

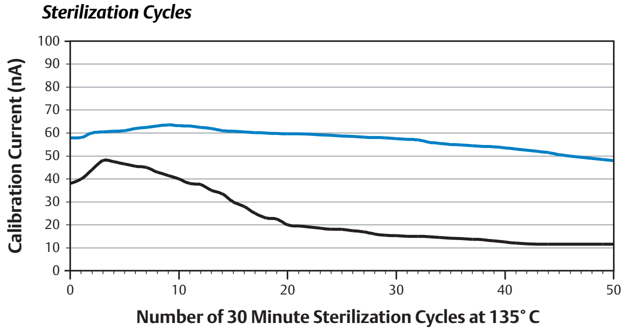
NIST Traceable Precalibrated Sanitary Conductivity Sensor Model 403VP with 16 micro inch Ra surface finish meets the life sciences demand for hygienic finishes

Fermentation

Dissolved oxygen and pH measurements in the fermentor are used to indicate the course of the fermentation process, ultimately influencing the growth of the culture, its cellular metabolism, and the quality of the final product. It is essential to employ accurate in-situ sensors in order to ensure optimization of these parameters to achieve high cellular productivity, resulting in high levels of recombinant product yield and concentration.

A typical batch fermentation process requires close monitoring and control of the pH and dissolved oxygen (DO) levels. Early in the process, inoculum from the seed fermentor is transferred to a production fermentation vessel and is grown in the presence of a carbon substrate, such as glycerol. pH control will commonly range from 4.5 to 6.0, depending on the mash formulation. In order to ensure the most favorable conditions for growth, the DO level is also carefully monitored so that the concentration of oxygen within the bioprocess does not fall below a specified value at which it becomes the limiting nutrient. Initially, the culture grows very slowly while adapting to the reactor environment. As the biomass of the culture increases and the rate of substrate consumption accelerates, the dissolved oxygen level of the medium steadily decreases until the carbon source has been exhausted.

Comparison of Dissolved Oxygen Sensor Performance vs. Number of Steam Sterilization Cycles



Xmt Transmitters with FOUNDATION® fieldbus communications protocol offer bi-directional, state-of-the-art diagnostics to maximize uptime

Hx Steam Sterilizable pH & DO Sensors and Insertion Assemblies ensure stable readings throughout the fermentation batch so the product will meet spec

After the initial adaptation period, the carbon substrate is typically switched to methanol or another substrate, depending on the specific process, in order to induce the production of recombinant product. During this high-growth phase, the culture grows exponentially, releasing enzymes as a by-product of the metabolic process, either intracellularly or into the medium. Upon completion of the fermentation cycle, the culture is now ready to be harvested of recombinant proteins and further purified for clinical trials and commercial products.

For superior DO and pH measurement and control in the fermentor, the Rosemount Analytical Hx Series sensors are ideal. They have been designed to meet the stringent requirements of today's users and better withstand the challenges inherent in fermentation process, such as high temperature and caustic exposure, to reduce maintenance costs and increase sensor life and measurement integrity.

The Hx Series DO sensor benefits are due to the unique design of the membrane through which oxygen diffuses. Most conventional DO probes use a thin membrane to ensure rapid response; however, this configuration does not provide lasting resistance to the high temperature conditions encountered during fermentation and/or steam sterilization. High temperature exposure causes the membranes to dry out and delaminate after 5 or more cycles, leading to increased maintenance and/or membrane replacement. Thin membranes are also more susceptible to error induced by changes in the flow rate, which affects the diffusion and subsequent current generated by the anode and cathode.

For this reason, the Hx Series DO sensors feature a proprietary double-layer, steel mesh reinforced membrane. This membrane allows for rapid diffusion to maintain fast response, while providing longer life and constant current, regardless of changes in flow, to guarantee measurement stability.

For difficult pH measurements, Hx Series pH Sensors feature the latest innovations in reference and electrolyte technology by providing bioprocesses with the unique, patented Tri-Triple reference technology. The Tri-triple reference is comprised of three overall reference junctions working together to help maintain a drift-free pH signal with the use of a special electrolyte solution to fight poisoning ions (i.e. proteins and sugars), even after numerous sterilization cycles.

Cleaning

Pharmaceutical and biotech processing utilize two forms of aggressive cleaning in order to ensure sterility is maintained, to avoid product contamination between batches and to ensure product quality.

The most common cleaning method is Steam-in-Place (SIP). SIP uses steam upwards of 131°C for a defined amount of time, dependent on organisms and vessel sizes, to destroy the organisms in the reactors, fermentors, and other process equipment in contact with the media.

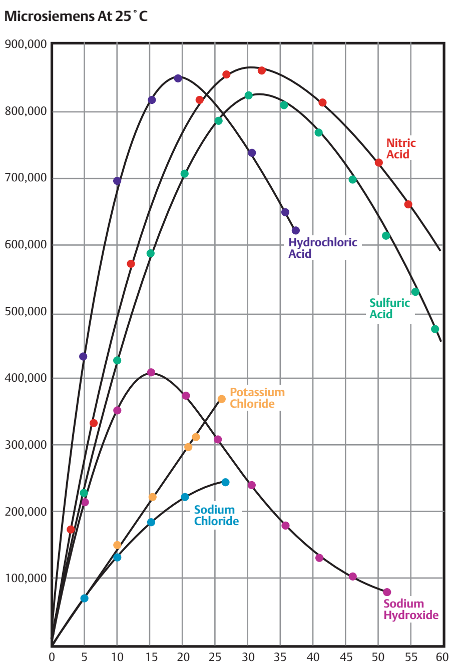


Figure 3. Concentration vs. Conductance of Sodium Hydroxide and Other Chemicals

The second method, which is growing in acceptance, is Clean-In-Place (CIP). CIP is an automated on-line process adopted from the food and dairy industry that utilizes a water rinse, typically followed by sodium hydroxide (NaOH), then an acid neutralization and/or an additional water rinse. To ensure effective cleaning via CIP, it is critical to monitor the acid strength. For this measurement, CIP-resistant, sanitary inductive conductivity probes are the ideal choice, because conductivity provides a direct correlation to concentration (see Figure 3).

Each of these cleaning processes creates special challenges for the in-situ pH and DO sensors. SIP cleaning dehydrates the glass pH electrode, hence reducing sensitivity and life, while the steam causes the dissolved oxygen membrane to dry out and delaminate, resulting in erroneous measurements. The CIP process is typically even more aggressive with respect to the sensors than SIP. The strong bases leach the pH glass of the primary active constituents — such as lithium — and, like steam, cause the pH

Model 225 Sensor with optional USP Class VI traceable materials offers the safest biocompatibility in your process

reading to become sluggish and inaccurate, greatly reducing life.

The dissolved oxygen sensor is also attacked. The membrane, which is designed to be selective to oxygen, denatures, resulting in increased interferences from other ions and eventual delamination. Therefore, it is important to select probes that have been designed to provide the greatest resistance to steam and chemical attack (see Figure 4).

It is also possible to automate the cleaning regimen using sanitary valves to isolate the sensor from the process, which, in addition, provides protection against drying between batches, extending sensor life.

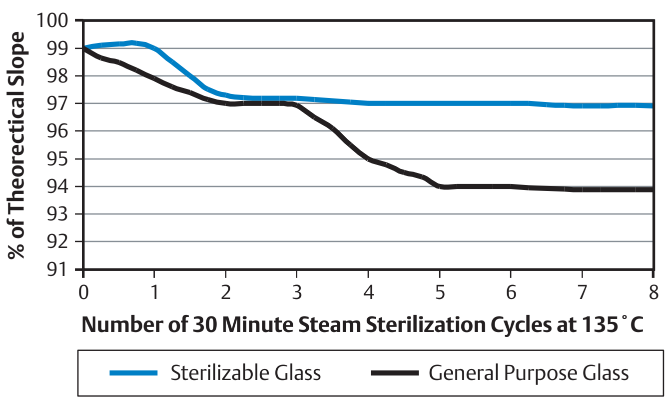


Figure 4. Comparison of pH Sensor Performance vs. Number of Steam Sterilization Cycles for General Purpose (Industrial) and Sterilizable Glass Formulations

Chemical Production

Electrochemical process control is important in several bulk chemical production processes including reactors, scrubbers, and separators. Several different types of electrochemical sensors may be applied to these processes – such as pH, to control acid addition; conductivity, to control the acid dosing strength; and ORP (redox), to indicate the extent of reaction or monitor a dechlorination process.

Due to the aggressive nature of the chemicals and the high temperatures and pressures commonly found in industrial chemical processes, it is recommended to use robust industrial sensors that provide improved resistance to process coating and fouling to ensure a stable and reliable signal.

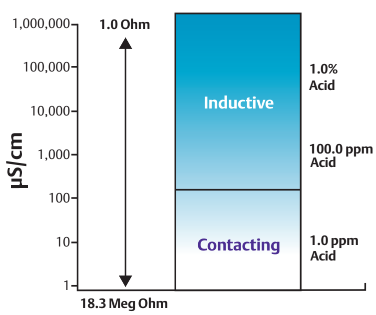


Figure 5. Conductivity sensor selection guideline

Industrial, Coating-Resistant TUpH pH Sensors

For conductivity, it is recommended to use inductive sensors for all applications except pure water (i.e., where the minimum conductivity is greater than 150 µS/cm- figure 5). For pH, it is best to use a rugged plastic composite sensor with a coating-resistant reference junction, and pH glass selected to meet the process needs. For example, many processes are controlled at 11 pH or higher, and in these cases it is critical to select a sodium-resistant glass to prevent sodium ion error. However, if the process is controlled below 11 pH, then general-purpose glass will be more than adequate.

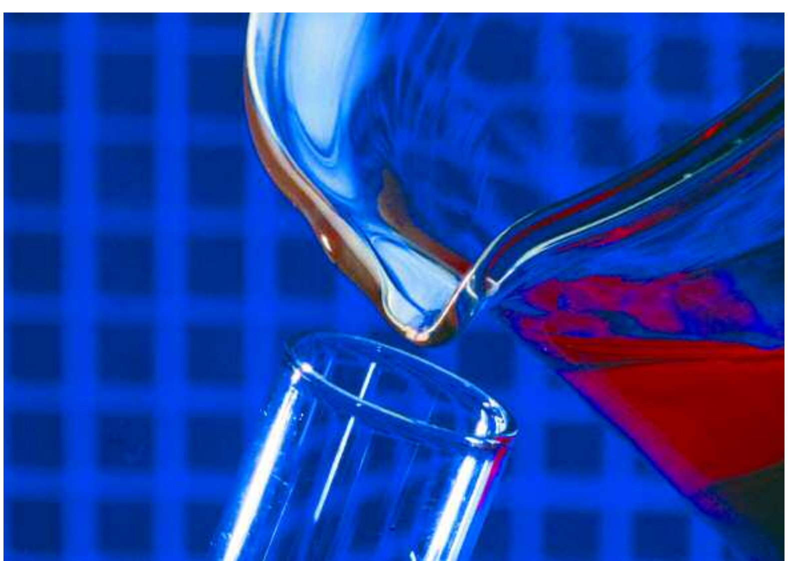
For the measurement of ozone, oxygen, or chlorine in chemical processes, it is not recommended to use a sterilizable DO sensor. Instead, select a more rugged sensor with a

Sanitary, coating-resistant inductive conductivity flow-through sensor Model 245

large electrolyte reservoir and install it in an area with constant agitation to provide a reliable signal. It is also recommended to use a jet spray cleaner or other automated cleaning technique to prevent build-up on the membrane.

Chemical processes seldom require steam sterilization. Cleaning regimens for chemical processes are typically manually performed — using water, weak acids, or detergents — according to a scheduled preventative maintenance program. In some cases where the potential for coating is high or corrosive chemicals are used, special holders and valves may be used to automate the cleaning sequence and/or eliminate operator exposure to harsh processes.

Industrial, Coating-Resistant Inductive Conductivity Sensors, Model 200 Series



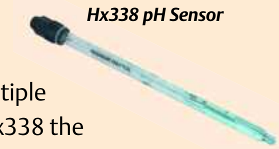
Purification

Liquid Chromatography is a popular technique for Purification, which is the process of separating specific protein molecules from the mother solution. Liquid chromatography consists of a fluid (mobile phase) carrying the mixture to be separated (sample) past or through a solid or gel (stationary phase). Chromatography separation technologies include gel filtration, ion exchange, hydrophobic interaction, and affinity.

Conductivity and pH, along with ultraviolet (UV) optical sensors, are critical measurements used to maximize yields, throughputs and protein purities. These sensors are used to activate valves for product collection and column regeneration, as well as monitoring clean-in-place cycles. Sensors must be highly accurate and fast responding. Wetted parts must be chemically compatible to withstand high salt and protein environments as well as CIP and SIP cleaning cycles. Wetted surface finishes must be minimized to ensure the separation process has been thoroughly completed and that no cross contamination occurs between batches. Sensors must be designed to fit into small line sizes in order to maximize flow rates and minimize pressure drops. In instances where sensors cannot fit directly into the line, a sampling side stream can be utilized.

The Model 245 Sanitary Flow Through Toroidal sensor (page 8) is ideal for end point determination through conductivity. The Model 245 comes in line sizes as small as 1/2". Wetted materials are 316L stainless steel, unfilled PEEK, and EP o-rings. An external RTD can be wired directly to the external junction box for fast and accurate temperature compensation. For processes where material leaching is a concern, choose the Model 225-08 Toroidal Conductivity sensor that is manufactured with raw material traceable to USP Class VI Bioreactivity standards.

The Model Hx338 sensor features the Tri-Triple reference technology. The pH sensors can withstand high protein and salt concentrations. The Hx338 can withstand multiple CIP and SIP cycles. These features make the Hx338 the ideal pH sensor for use in the purification process.



Steam-sterilizable Hx338 pH Sensor

Waste Treatment

The Pharmaceutical industry has specialized needs for monitoring and treating waste effluent. Fermentation processes, in particular, may result in waste that requires biological inactivation to prevent the escape of viable cells into the environment.

Coating-Resistant pH Sensor, Model 396P Installed in a Jet Spray Assembly for Automated Cleaning

Biological waste may be combined with spent media, floor washings, and laboratory waste. Such waste often contains high levels of organic materials and high BOD (biological oxidant demand), requiring additional treatment steps.

High BOD waste is treated using anaerobic digestion, controlled aeration and sand filters before being combined with effluent from reactors, mixing tanks, and process rinse water in a central wastewater facility. Common processes – such as clarification and sludge removal, aeration basins, gas strippers, heavy metal removal, chlorination, and dechlorination – are then used to prepare the wastewater for release. The exact treatment methods depend on the nature of the plant operation and on the local environmental regulations. pH, ORP, electrical conductivity and amperometric measurements, (chlorine residual, ozone and dissolved oxygen) ensure adequate effluent treatment.

Residual chlorine measurement is especially important in ensuring final disinfection of the water. An amperometric sensor completes the measurement by consuming (i.e. reducing) the specie of interest at the cathode to produce a current which is proportional to the concentration. For maintenance intensive processes, such as activated sludge, an automatic jet spray is recommended.

Industrial Amperometric (DO, Ozone, and Chlorine) Sensor for Waste Treatment Processes, Model 499A Series

Solu Comp II, Multi-parameter Analyzer Model 1055

Rosemount Analytical Instrumentation

The optimum solution for the process relies most heavily on selecting the right sensor to match the process needs. In most cases the instrument is simple to select and depends on the power, control, and communication requirements, in addition to other desired features, such as HART® and preventative diagnostics. Choose the one that meets your needs. Pharmaceutical production can especially benefit from FOUNDATION® fieldbus devices, offering electronic data capture for calibration and configuration changes per 21 CFR Part 11. New plant start-ups are accelerated with smart, bi-directional transmitters.




Features	SoluComp II, 1055 Series	54e Series	5081 Series	SoluComp Xmt Series
Power Requirement	115 - 230 VAC or 24 VDC*	115 - 230 VAC or 24 VDC	24 VDC	24 VDC
Number of Sensor Inputs	Two	One	One	One
Number of 4-20 mA Outputs	Two	Two	One	One
Available Measurements	Select any two: pH, ORP, Conductivity, Resistivity, Dissolved Oxygen, Ozone, Chlorine, Flow, Turbidity	Select one: pH, ORP, Conductivity, Resistivity, Dissolved Oxygen, Ozone, Chlorine	Select one: pH, ORP, Conductivity, Resistivity, Dissolved Oxygen, Ozone, Chlorine	Select one: pH, ORP, Conductivity, Resistivity, Dissolved Oxygen, Ozone, Chlorine
HART Compatible	No	Yes	Yes	Yes
FOUNDATION Fieldbus Compatible	No	No	Yes	Yes
Multi-lingual	Yes	Yes	No	No
Relays	3	4	0	0
PID Control	No	Yes	Yes/Ff	Yes/Ff
Advanced Diagnostics Capability	Some	Complete	Complete	Complete
Area Classifications	Class I, Div. II	Class I, Div. II	Class I, Div. I and Div. II, Explosion proof	Class I, Div. I and Div. II
Available Approvals	FM, CSA, CE, UL*	FM, CSA, CE	FM, CSA, CE, ATEX	FM, CSA, CE, ATEX

* Not available for Turbidity

Emerson Process Management: The Proven Source

Emerson Process Management is the proven supplier of Rosemount Analytical on-line electrochemical sensors and instrumentation with over 60 years experience in process control and waste treatment. In recognition of our dedication to customer service, product excellence, and quality, we have received the #1 Readers Choice Award from Control Magazine for the eleventh consecutive year.

Incorporating a properly defined and validated water system will benefit pharmaceutical and biotechnology companies through quality control, and by reducing capital costs, lifetime maintenance costs and monitoring costs.

Accurate, on-line electrochemical measurements, such as pH, dissolved oxygen, conductivity, chlorine, and ozone, provide substantial improvements in the level of process control, quality, efficiency, and profitability that can be achieved in pharmaceutical bioprocessing. These measurements also play a critical role in meeting regulatory compliance at the local and federal level. Count on Emerson for the systems and solutions you need in an ever-changing, dynamic world. See us on the web at ***RAIhome.com.***

PlantWeb® Brings It All Together

Rosemount Analytical's instruments are part of Emerson Process Management's PlantWeb® field-based architecture: a scalable way to use open and interoperable devices and systems to build process solutions. The PlantWeb architecture consists of intelligent field devices, scalable platforms and standards, and integrated modular software, all working together to create, capture, use, and distribute information and process control data.

This architecture can reduce your capital and engineering costs, reduce operations and maintenance costs, increase process availability, reduce process variability, and streamline regulatory reporting. When combined with Foundation fieldbus, new plants get the benefits of accelerated plant start-ups due to less wiring demands and easier analyzer configurations.

To see what PlantWeb can do for *your* operation, call or visit us at ***PlantWeb.com/RunSafe***

Offices Worldwide

Emerson Process Management's field sales offices are your source for more information on the full line of Rosemount Analytical products. Field sales personnel will work closely with you to supply technical data and application information.

For more information on any of the products listed in this brochure and their applications, please contact your nearest Rosemount Analytical sales office. To request copies of our literature, call 800.854.8257 or visit our website.

www.raihome.com

Online ordering available.

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Emerson's Rosemount Analytical Liquid Division provides technologies and services for the analysis of liquid processes. For a wide range of applications, Emerson provides more than 60 years of expertise in high-precision analytical sensors, instrumentation and services. For information, call 800.854.8257.

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