



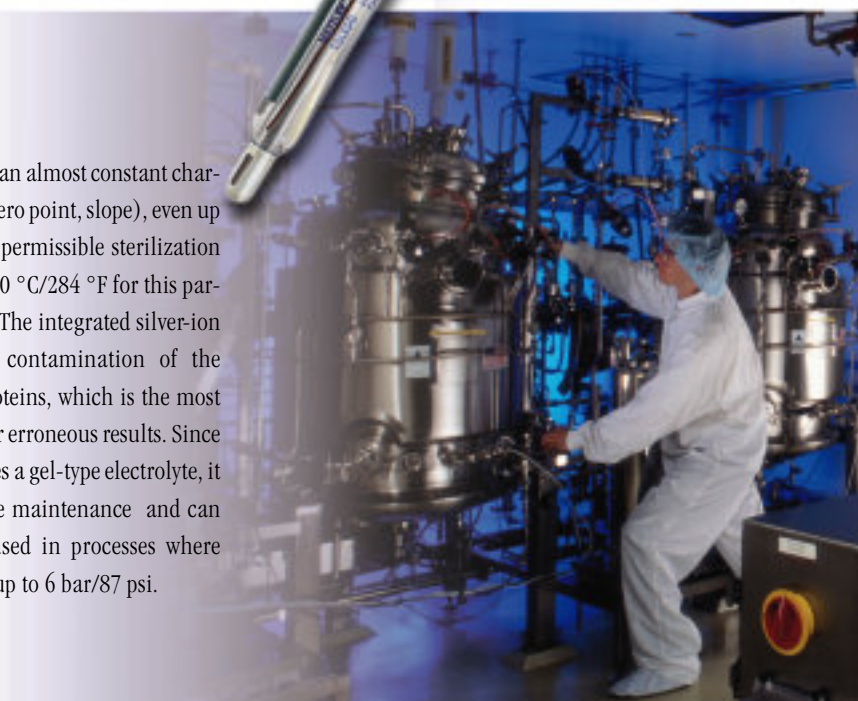
Reliable pH control in fermentation processes

pH is a critical parameter to monitor during biotechnology fermentation processes because it has a profound influence on the growth characteristics of the microorganisms/biomass. Backed by more than 50 years of pH experience, METTLER TOLEDO Ingold is at the forefront of innovation and product performance for the pharmaceutical industry. All of our products are designed to maximize your up-time because we pay attention to the most intricate details which affect reliability, accuracy, and hygienic design.

Long-term reliability and stability

pH electrodes must be calibrated prior to being sterilized or autoclaved, because contact with any non-sterile solution after sterilization renders the sensor useless for sterile process. Obviously, this is a rhetorical statement, but it underscores the importance of having a stable reference system which can endure the intense conditions of sterilization, which generally requires direct contact with steam for 30 minutes at 121 °C/250 °F. Ingold's unique membrane glass and reference systems excel under the most demanding sterilization protocols. The InPro® 3100

electrode displays an almost constant characteristic curve (zero point, slope), even up to the maximum permissible sterilization temperature of 140 °C/284 °F for this particular electrode. The integrated silver-ion barrier prevents contamination of the diaphragm by proteins, which is the most common cause for erroneous results. Since the InPro3100 uses a gel-type electrolyte, it requires very little maintenance and can be successfully used in processes where pressure reaches up to 6 bar/87 psi.



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FDA conformity

All wetted materials conform with FDA (Food and Drug Administration) guidelines for use in pharmaceutical production and food processing. Certificates of compliance are available upon request. ■

Specifications	InPro 3100
pH range	0...14
Temperature range	0...140 °C, 32...284 °F
Pressure range	0...6 bar, 0...87 psi
Temperature sensor	Pt100 or Pt1000
Connector	VarioPin (IP68)
Sterilizable	yes
Autoclavable	yes
Lengths	120, 150, 225, 325, 425 mm
Use in hazardous areas	Zones 2, 1 and 0
Certification	PED 97/23/EEC, Art.3, Para.3 Ex II 1/2G EEx ia IIC T6/T5/T4

Our measurement system is down!

“The new electrode is not working!” Occasionally our inside technical staff is confronted by calls of this nature. However, more often than not, the fix is usually something quite simple.

One of the first diagnostic procedures is to check for the “watering cap” and make sure it has been removed. All newly manufactured electrodes are equipped with a small plastic watering cap placed over the sensor end to prevent the gel layer of the membrane glass from drying out. If the cap remains on the electrode, no measurements can be taken. When scrambling to keep production running, it is easy to overlook the watering cap- but this one is a fast and easy fix ! ■



Growth control of biomass using turbidity measurement

Optical density systems for in-line biomass concentration measurement can provide significant time-savings in production. METTLER TOLEDO has the right solution.

Medicines containing purified antigen are produced through classical aerobic bacteria fermentation. For fermentations from an initially fully clear and particle-free medium, the cell growth can be monitored with an optical turbidity system.

Process

In the present case the process suffered from inefficient yield with uneven final quality, as first fermentation step ended in the night but seed culture was not transferred to the production fermenter until the morning. Furthermore, the production fermentation was terminated through a timer rather than when the correct yield had been achieved.

Production scale

Two-stage fermentation in a 100 l seed fermenter and a 1000 l production fermenter with a fermentation time of 48 hours were used.

After the installation of a turbidity system for inline biomass concentration measurement, notable time-savings were achieved in production. Up to a total of one day was gained in this two-stage fermentation process. The fermenters could therefore be used more efficiently, and the production capacity increased without the installation of additional fermenters.

More accurate control of the fermentation further led to an increase in yield of 5 to 10%, depending upon the culture in-

volved, and also to a more consistent and reproducible quality.

METTLER TOLEDO solution

Two standard stainless steel turbidity sensors InPro 8200 were installed, one in each fermenter. Kalrez-FDA seals were used to better withstand sterilization and CIP conditions. Traditional side entry mounting was selected for fermenters using InFit®761 housings. The sensors were connected to Trb 8300 transmitters.

First the zero point, was adjusted in the clear solution before fermentation. Empirically established values for gain and turbidity development during the fermentation for the different products had been carefully studied on a smaller scale and the values found were entered directly into the transmitter. If necessary, these values (zero and gain) were adjusted after the first cycles in the fermenter. Optimal final turbidity values of the respective fermentation (corresponding to the optimal fermentation yield) were set. This allowed transfer of the medium from the seed fermenter to the production fermenter to be carried out fully automatically at the opportune moment, and the final fermentation stage to be interrupted at the optimal point of time. ■



Turbidity Transmitter Trb 8300.



Housing InFit 761, with installed turbidity sensor InPro 8200.

SensoCheck[®] provides maximum process reliability

The Premium and Advanced Line pH transmitters from METTLER TOLEDO Ingold are able to monitor serviceability of the pH electrode during calibration procedures and during actual process operation. The new multifunctional pH sensor InPro[®]3200SG with an integrated ancillary platinum electrode is ideal for use in conjunction with the diagnostic features of the Premium and Advanced transmitter series.

Self-diagnostics during pH measurement

During calibration, SensoCheck continuously monitors the electrode relative to its zero point, slope and response. On the basis of this data, a calculation of the performance efficiency of the electrode is derived. A specialized function of SensoCheck is impedance measurements of the glass electrode (resistance at the glass membrane) and the impedance of the reference electrode (resistance at the diaphragm). This is accomplished by superimposing an AC signal between glass electrode and reference electrode as well as between reference electrode and an ancillary electrode, against which the ohmic resistance of the glass membrane and reference system are both measured. Fig.1 illustrates the measurement system setup when using a separate, auxiliary electrode.

This innovative diagnostic tool enables the pH electrode to be monitored for possible glass breakage or contamination during operation. Instead of using a cumbersome auxiliary electrode, SensoCheck makes it possible to create the required electrical contact via the vessel or pipe wall, or even the housing – provided that the distance to the electrode is not too great and that the conductivity of the sample media is not too low.

NEW: InPro3200SG with integrated ancillary electrode

In addition to a temperature (Pt100 or Pr1000), the new multifunctional electrode InPro3200SG is equipped with an ancillary platinum electrode (guard ring).

- to monitor the impedance of the reference electrode
- to ground the sample medium in the event of problems arising from noise
- to carry out simultaneous ORP measurements

Fig.2 illustrates the measurement setup for the InPro3200SG. This sensor performs equally well in biotechnological or in chemical applications. It is sterilizable, autoclavable and certified for use in hazardous areas (Zones 2, 1 and 0). The mechanical pressure resistance has been tested and certified in accordance with the current European Pressure Equipment Directive (PED 97/23/EEC, Art.3, Para.3).

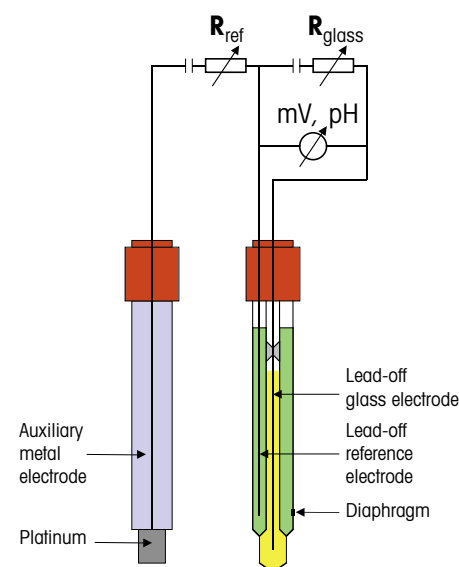


Fig. 1: Monitoring of impedances of glass and reference electrodes with the aid of a separate, auxiliary electrode.

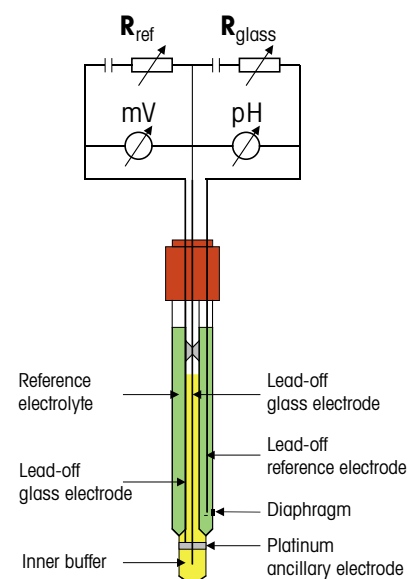


Fig. 2: Monitoring of the impedances of glass and reference electrodes using the multifunctional pH sensor, InPro3200SG.

Specifications	InPro 3200SG
pH range	0...14
Temperature range	0...140 °C, 32...284 °F
Pressure range	0...2.5 bar, 0...72 psi
Sterilizable	yes
Autoclavable	yes
Temperature sensor	Pt100 or Pt1000
Reference system	ARGENTHAL® with silver-ion barrier
Overall lengths	120, 225, 325, 425 mm
Connector	VarioPin VP (IP68)
Hazard rating	Ex II 1/2G EEx ia IIC T6/T5/T4
Pressure certification	PED 97/23/EEC, Art.3, Para.3

Transmitter functionalities

Built-in alarm functions of these transmitters are easily configured to respond to an over-range or under-range condition of user defined parameter limit values, which first triggers a warning signal, subsequently followed by indication of a system failure. A membrane resistance of 0 might signify glass breakage, or any excessive resistance at the reference electrode points caused by fouling of the diaphragm.

Monitoring of the pH electrode relative to the impedances of the glass and reference electrodes allows for maintenance to be conducted in real time, before the unexpected failure of the loop. During set up, the electrode configuration (type of glass membrane, type of reference system) as well as the process conditions must be taken into consideration, since the ambient temperature has a direct effect upon the electrical resistance of the glass membrane (which increases relative to a decline in temperature).

Cost savings through automation

Contamination at the diaphragm is the most common cause of erroneous pH readings. By monitoring the impedance of the reference electrode, it is possible to predict the level of fouling. Once a user defined limit has been reached, the sensor can be automatically cleaned and calibrated without human intervention by the METTLER TOLEDO EasyClean 350 automated cleaning system. The EasyClean systems use safe and effective pneumatic technology to control multi-functional retractable housings to withdraw the sensor from the process and position the sensor for automated flushing, cleaning, calibration, and reinsertion into the process afterwards.

Monitoring and automation of a pH measuring point provides substantial operational benefits and cost savings:

- longer serviceable life of the electrodes due to regular cleaning, and therefore lower electrode consumption
- reduced labor costs through automation of routine maintenance tasks
- more accurate pH measurements due to regular cleaning and recalibration of the electrode

Self-monitoring and automation of a pH measuring point is therefore an important factor for achieving greater process reliability. ■



InPro3200SG – the new multifunctional pH sensor with integrated platinum electrode.



Premium Line Transmitter with 4-wire design is used for highly exacting measurement and control tasks.

Impedance of reference electrode

Electrode model	Warning		Failure	
	min.	max.	min.	max.
465, InPro2000	2 k	15 k	1 k	20 k
XEROLYT	5 k	20 k	1 k	30 k
InPro3100	12 k	50 k	5 k	60 k
InPro4200				
InPro4800				
PA, DPA, DPAS, InPro3200(SG)	2 k	10 k	1 k	20 k

Impedance of glass membrane

Membrane type	Warning		Failure	
	min.	max.	min.	max.
HA	200 M	800 M	0 M	1000 M
A41, LR3	100 M	600 M	0 M	800 M
LoT, HF	50 M	200 M	0 M	400 M



Automated cleaning and calibration with EasyClean.

InTrac 798 – for the most demanding hygienic requirements

With the InTrac798, METTLER TOLEDO Ingold introduces a new retractable housing for the pharmaceutical and food industries. Increasing demands for hygienic equipment design and the need to access the sensor at any time, have led to the development of this advanced housing model.

This completely new housing raises the bar for sanitary design. The InTrac 798 is certified in accordance with EHEDG and 3-A guidelines. It is equipped with a state-of-the-art flushing chamber designed to optimize cleanability. The unit is outstanding for its array of advanced features such as:

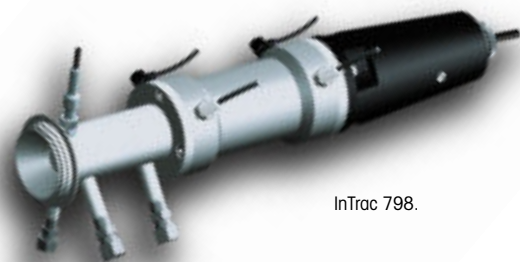
- totally drainable flushing chamber due to the positioning of the O-ring
- use of 12 mm sensors of uniform length (120 mm)
- suitability for applications in the food processing and pharmaceutical indus-

tries, using tested and EHEDG-certified process connectors such as Tuchenhagen Varivent, Neumo-BioControl, Tri-Clamp, and Ingold cap nut.

- safe steam sterilization of the sensor in the flushing chamber
- process connector and flushing chamber formed from a single piece of stainless steel
- complete absence of crevices and slits
- fully hygienic cleaning
- standard use of FDA-compliant EPDM

for all wetted O-rings (other materials on request)

The hygienic process connection (flange) and drainable flushing chamber are ingeniously combined in one single element, to make this retractable housing a real innovation in its field. ■



InTrac 798.

New membrane shape for optimal pH measurement

The shape of the membrane of METTLER TOLEDO pH sensors with HA glass membrane has been redesigned to improve measurement characteristics and handling. The HA membrane glass is resistant to high-alkaline solutions and therefore ideal for measurements in media with high pH values. It can also withstand elevated temperatures. The alkaline error is minimal, and reliable results are assured under particularly critical operating conditions.

NEW: spherical membrane

The change from the previous cylindrical form of the HA glass membrane to a spherical form is accompanied by a number of important advantages:

- greater mechanical stability
- improved cleanability of the sensor
- eliminating air bubbles in the inner buffer

More rapid response of temperature sensor

The position of the temperature sensor has also been changed. The Pt100 or Pt1000 is now more optimally situated directly in the inner buffer behind the glass membrane, resulting in some further advantages:

- more rapid response of the temperature sensor
- more precise temperature measurement
- more exact temperature compensation

The pH electrode InPro3200 is fully sterilizable and autoclavable, as well as being ideally suited for biotech, food and chemical applications. ■

FDA-compliant quality and services – making the difference

High product quality in pharmaceutical applications can only be achieved if all the relevant steps of a process are carefully defined and measuring results are precise and reproducible. Complete documentation of each single step is of highest priority. METTLER TOLEDO has the knowledge to assist in equipment qualification (EQ) to meet the most stringent legal regulations.

Design qualification (DQ)

In this very first step, the functional, operational and technical specification for a measuring point have to be defined. METTLER TOLEDO offers the requested certificates to prove product quality.

Installation qualification (IQ)

Following basic installation and initial calibration, the measuring loop is ready for testing. All relevant data will be recorded in the EQ document provided by METTLER TOLEDO service personnel.

Operational qualification (OQ)

Before used in the process, the guaranteed performance has to be checked and recorded in the EQ document. A detailed operational qualification is the final touchstone for successful system functionality.

Performance qualification (PQ)

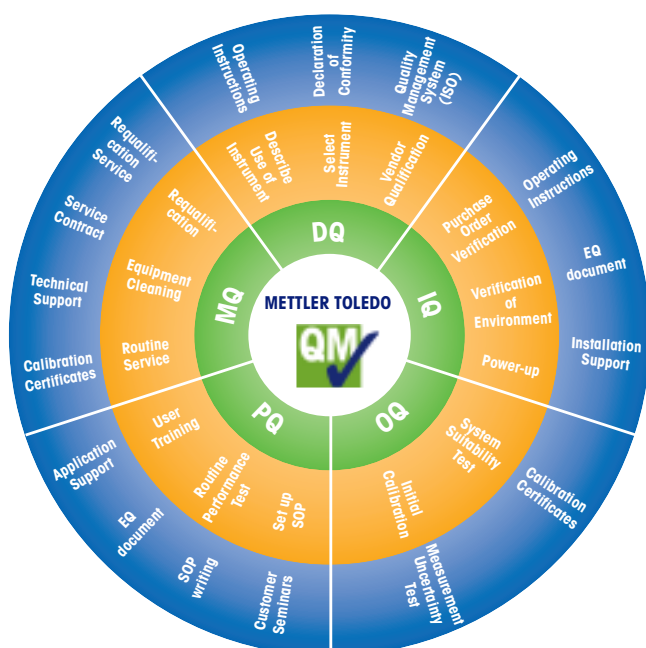
Periodically performed system tests guarantee proper functionality of a measuring loop. Results are protocolled in the log-book and are key information for a traceable validation.

Maintenance qualification (MQ)

METTLER TOLEDO will train personnel to set up a preventive maintenance plan, indispensable for ensuring trouble-free process operation.

Compliance tools and services are available as individual modules or comprehensive packages.

With this package METTLER TOLEDO is able to provide customized validation services. ■



Global services

- Conductivity sensor calibration (NIST traceable)
- NIST traceable buffers
- Validation support/consulting
- Equipment qualification according to the latest QM standards as defined by the responsible authority
- Sensor performance qualification

METTLER TOLEDO meets the latest standards of GMP and FDA guidelines.

Oxygen, conductivity and pH transmitters with PROFIBUS®PA interface

For some years, METTLER TOLEDO has been offering transmitters with HART® Communication which superimposes a digital signal on the customary 4 - 20 mA DC analog signal. This enables the transfer of additional information than just a measurement signal.

From now on, transmitter units are also available which incorporate a fully digital PROFIBUS PA interface according to the "Profile for Analytical Devices, Version 3", suitable for measurement of dissolved oxygen, electrolytic conductivity (conductive and inductive) and pH value.

Simple connection to the PCS through Plug & Play.

Connection to the PROFIBUS DP level is possible either by direct linkage or through a segment coupler. The instrument interface employs the FISCO model to ensure intrinsically safe networks. The existing well-proven functions such as automatic calibration (Calimatic®), sensor diagnostics (SensoCheck®) and parameterization can be accessed via the PCS just as easily and comfortably as before. ■



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