Fully Automatic pH Sensor Calibration – Now Also Available for Upstream Process Requirements

A breakthrough thanks to proven cleanability and sterilisability

Are you aware that manual calibration of pH sensors is one of the biggest risks for batch losses?

Calibration and verification of pH sensors in biopharmaceutical production are performed before and after each batch. The calibration procedure is usually done manually, which involves considerable time and personnel costs due to the removal and installation of sensors, calibration and documentation, resulting in correspondingly long plant downtimes.

Knick's automation solutions have been in use for years in other industries and in pharmaceutical downstream processes, cleaning and calibrating sensors around the clock, twenty-four seven, without manual intervention. In the upstream sector, the systems have so far only been used in buffer production. This could now change, as Knick has certified that the sensor in the SensoGate retractable fitting, including all process-wetted surfaces and seals, can be cleaned in accordance with ISO 15883-3 and sterilised in accordance with ISO 17665-1.

This finally allows fully automated pH measuring points to be implemented in cell cultures and fermentation processes, minimising the risk of human influence, reducing plant downtime between batches and enabling reproducible calibrations with more accurate pH values.

Risks and Limitations of Manual pH Calibration in Batch Operation, Including Considerations for Accuracy, Precision, and Consistency

The upstream process of cell cultures is complex, expensive and time-consuming. The parameters of pH and dissolved oxygen

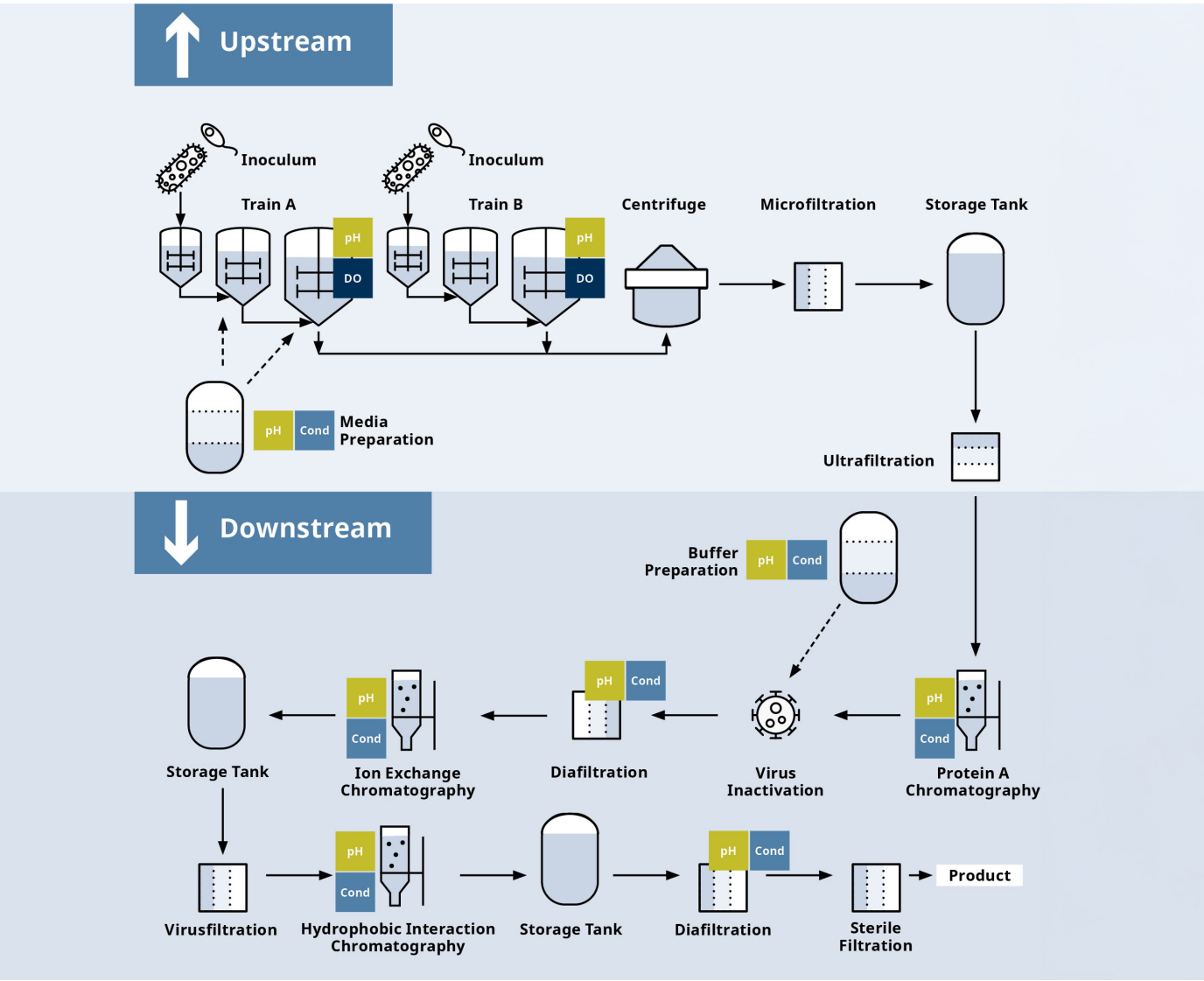

Figure 1: Process diagram with measuring points

Figure 2: Retractable fitting SensoGate WA131H with a customised bevelled clamp connection

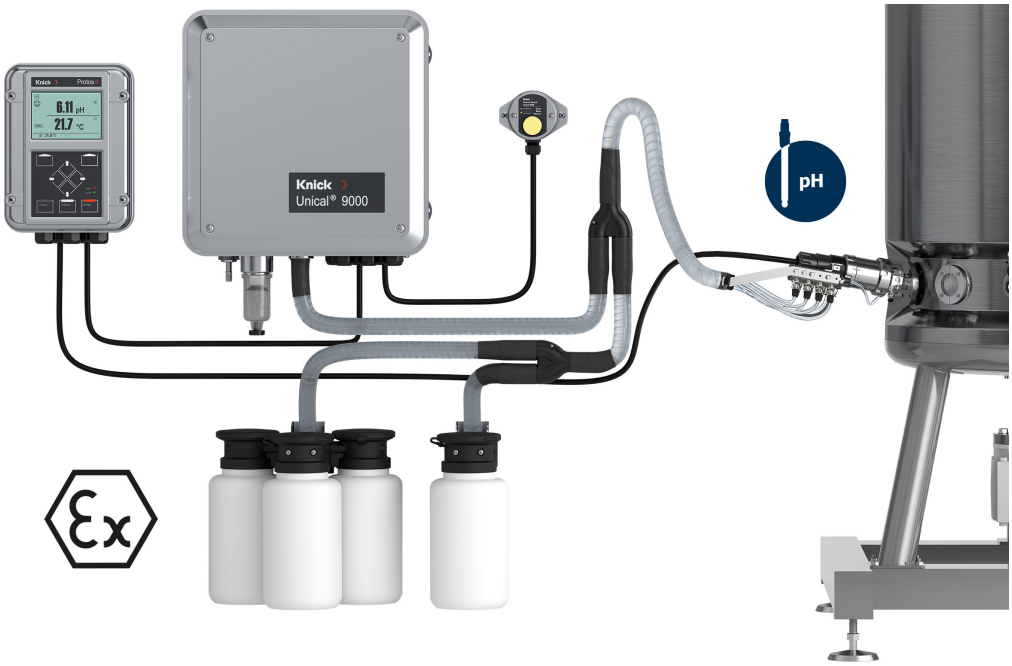

Figure 3: cCare – fully automated sensor maintenance system for cleaning, calibration and conservation

must be strictly controlled and monitored to ensure compliance with optimal cell growth conditions and maximum product quality and quantity. During the process, outside interventions are not permitted since the risk of contamination is too great and would possibly result in the loss of the batch.

This makes it even more important to have reliable pH values available at all times. But at the same time, pH measuring points require intensive maintenance. In many processes and media, sensors must be cleaned and calibrated several times a day. This minimises sensor drift and delivers measured values that can be trusted.

It must be ensured that the measurement technology used during the process operate flawlessly. This is accomplished through pre-batch calibration and adjustment and post-batch verification, all of which must be documented according to GMP guidelines.

However, many companies still calibrate pH sensors manually. The calibration process is very time-consuming, requiring an employee to "invade" the cleanroom, remove the sensor, clean it, place it in a series of different buffer solutions and wait until the pH value is stable.

This poses the risk of mechanical damage to the sensor, and the employee's actions may also influence the process. For example, whether the sensor is swirled or simply immersed in the buffer solution makes a big difference. Finally, the sensor must be reinstalled, cleaned and/or sanitised. A risk assessment at a customer's facility identified more than 80 potential sources of error during calibration and measured value transmission.

The time required to do this, in an era characterised by staff shortages, possible transmission errors in the case of manual work steps and the subsequent mistake of rejecting batches, makes it essential to start thinking about optimisation activities supported by automation.

Automatic, Standardised pH Sensor Calibration

Knick offers a solution for automatic pH sensor maintenance that eliminates the disadvantages of manual calibration. The system of automatic pH measuring loops, which Knick markets under the name "cCare", performs a standardised calibration fully automatically and sends all values and the calibration report to the process control system. cCare is a modular system and consists of an electro-pneumatic controller, a retractable fitting SensoGate and a Protos transmitter.

The Protos II 4400(X) is the first industrial transmitter that fully automates audit trail requirements in accordance with FDA 21 CFR Part 11, ALCOA++, and EU GMP Annex 11 down to the field level. Remote login with two-factor authentication, transfer of all audit trail records and transfer of comprehensive calibration logs to the company database can be implemented using the proven PROFIBUS PA or PROFINET fieldbus protocols.

The cCare system is completed by media containers with integrated pneumatic metering pumps. The SensoGate retractable fitting is adaptable to individual installation situations through many process connections and immersion lengths.

The cCare system is also the only sensor maintenance system on the market that is fully approved for use in Zone 1 hazardous locations.

cCare does more than just extend sensor service life and reduce labour costs. Its fully automated sequences also ensure more accurate pH measurements, which directly impact the safety and yield of the biopharmaceutical process.

SensoGate – Best Retractable Fitting for Hygienic Requirements

An automatic sensor maintenance system requires a retractable fitting that allows the sensor to be moved into a rinsing and calibration chamber for maintenance. It is important to ensure that the process is safely separated and that no contamination

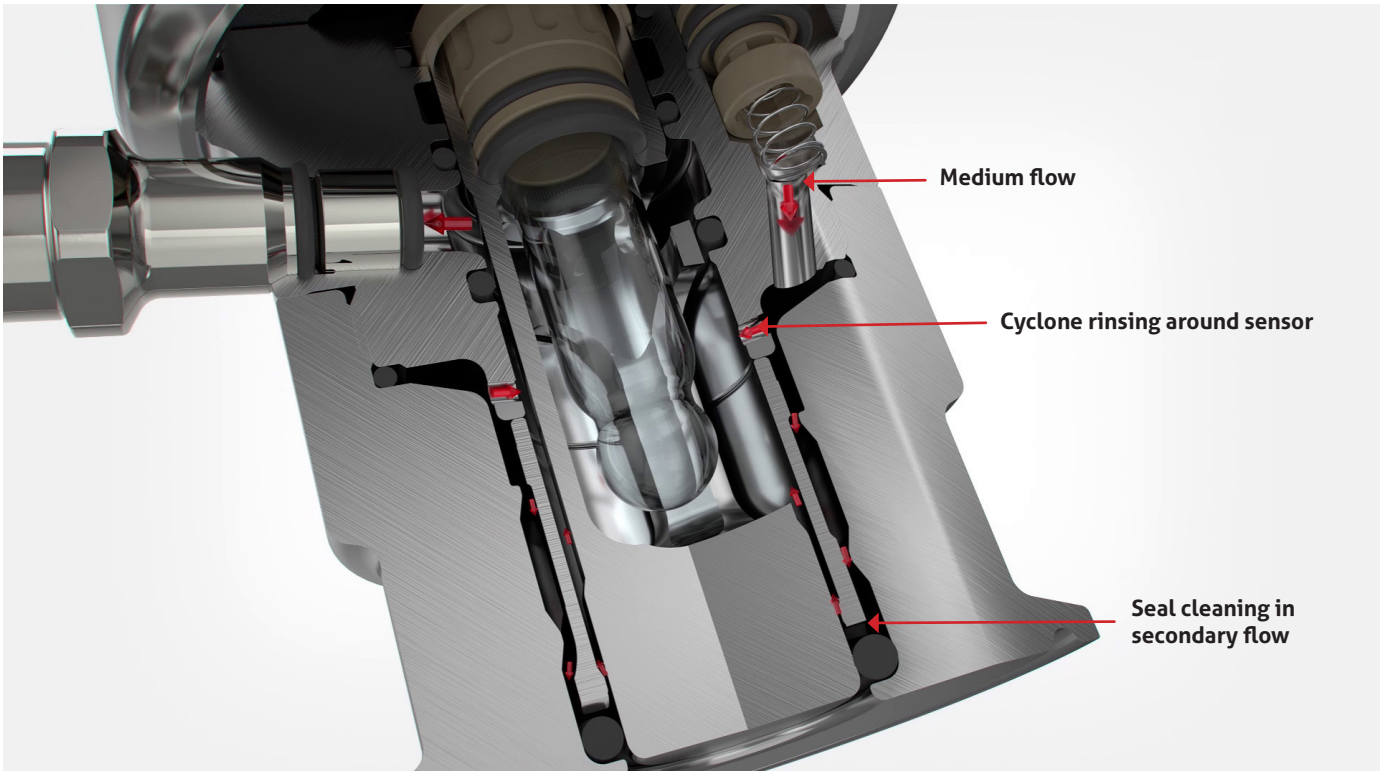

Figure 4: Interior view of the calibration chamber with cyclone rinsing of the sensor and secondary flow for the immersion tube's seal

can occur due to the transfer of medium or soiling when moving back into the process position.

Hygienic by design, the retractable fitting SensoGate WA131(M)H was developed from the ground up for pharmaceutical applications and is based on the most stringent standards available.

Its patented lock-gate system reliably seals the process at all times, allowing the sensor to be replaced without process interruption. A sophisticated cyclone rinsing thoroughly cleans the sensor, the seals and the calibration chamber. Unlike other manufacturers' retractable fittings, the SensoGate has no dead spaces that cannot be cleaned by rinsing, SIP and CIP.

Test Proves the SensoGate WA131H's Ability to be Used in Upstream Applications

Years ago, SensoGate was tested in a laboratory in accordance with EHEDG, where no bacteria survived in the internal and external process-side parts of the SensoGate retractable fittings during in-line steam sterilisation at 121 °C for 30 minutes.

Knick has now had SensoGate tested to meet even stricter requirements for biopharmaceutical applications. The focus was not only on killing germs and bacteria, but also on cleanability.

The SensoGate was validated by Test Labs Ltd (Peterborough, UK), a UKAS-accredited laboratory specialising in medical device testing. This choice was deliberate; Test Labs applies only medical device standards, thereby ensuring a level of validation that far exceeds industry standards. The co-operation with SGS Germany as a German partner ensures that the validation results are also fully recognised in the European regulatory context. This dual-site validation offers pharmaceutical operators additional safety for multinational regulatory submissions.

The cleaning test according to ISO 15883-5 simulated extreme soiling and was passed impressively by the SensoGate, even with deliberately limited cleaning.

Sterilisation validation according to ISO 17665-1 used one of the most temperature-resistant microorganisms known. The test results far exceeded expectations, and not only safely achieved the required Sterility Assurance Level (SAL), but also a safety margin that far exceeds pharmaceutical requirements.

The test has thus demonstrated that the retractable fitting can be used safely also in upstream processes.

Knick provides users with the test results and resulting recommendations for cleaning and sterilisation. This will help reducing the validation time required by the operator for regulatory purposes.

Dr. Michael Kogej

Dr. Michael Kogej, PhD chemist from the University of Bonn with a focus on instrumental analysis, began his career managing an industrial analysis laboratory. He later held product management roles at Mettler Toledo in process analytics before joining Knick Elektronische Messgeräte GmbH. Here, his hands-on experience in the field as Head of Application & Service now shapes his position as Global Market Manager, driving innovative process analytics solutions worldwide.