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Instrument Technology Moves into Bioprocess Development Laboratories

By Ravi Shankar

The same sensor instrumentation can now be used in process development laboratories, clinical trials, pilot plants, and large-scale manufacturing—thus simplifying product development, scale-up, and regulatory record-keeping.

Introduction

Regulatory authorities require biopharmaceutical manufacturers to continuously review and improve instrument calibration and verification procedures. Compliance is checked at regular intervals by external inspectors to ensure the quality of the process and subsequently, patient safety.

Compliance is required at all stages of drug development including lab-scale process development (PD), clinical trials, pilot plants, and large-scale manufacturing. If a drug

company uses different instruments—for example, pH sensors—at each stage, it has to keep records on each one, and then integrate new sensors into the next stage of the process. Today, modern instruments have built-in technology to simplify compliance and verification, making it possible to use the same pH sensor at all stages of drug development.

Laboratory vs. Production Plant Calibrations

Typically, the development of a biologic drug and its manufacturing begins in a PD lab where the manufacturing process is tested in small quantities, such as 0.5–5 litre batch sizes (**Figure 1**). Then the process moves to a small pilot-scale plant for testing the process with larger batch sizes of 10–50 litres. When pilot plant testing is completed, the process is scaled up to a full manufacturing plant.

At each stage in the development, various instruments—such as pH and conductivity sensors—are employed to analyze and control the process, and these must be calibrated and verified on a regular basis.

Legal requirements for regular checks on analytical sensors are commonly fulfilled with “wet calibration” where

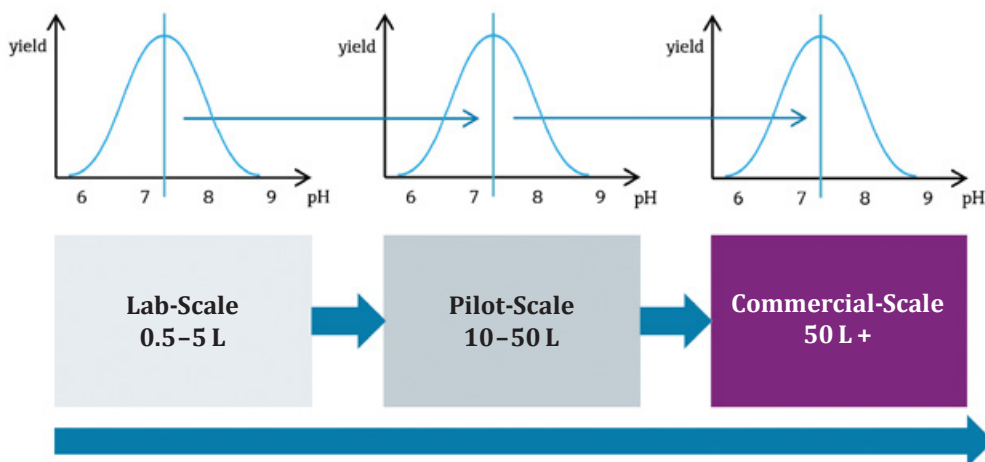


FIGURE 1. Typical batch sizes in biologic drug development.

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a pH or conductivity sensor is immersed in a reference solution and checked for accuracy.

Wet calibrations are easily done in a laboratory environment (**Figure 2**). The environment is controlled, the sensor is easy to access, and the necessary equipment is at hand. For example, an analog-based pH measurement system must be managed at its point of use with the sensor, cable, and transmitter calibrated together. An analog pH probe generates a small mV signal measured by the transmitter and converted to pH by a calibration routine residing in the transmitter. Any physical variation in the sensor, or between the sensor and the transmitter, will result in deviation of the measured value.

A lab system is typically validated and calibrated under controlled conditions. This is not always true of a production system, so the same pH sensor and calibration procedure used in a lab may not work in a commercial-scale production plant.

The downside of wet calibrations in a biopharmaceutical manufacturing plant is that the instruments typically have to be removed from the process (**Figure 3**) and sent to a laboratory. After calibration, the instrument is then installed again. Undetected damage during transport or handling can lead to a situation where a recently calibrated instrument is not performing according to specifications.

Alternatively, a mobile calibration cart can be used to perform an on-site calibration. This method typically eliminates the need for dismounting the sensor being tested, but still requires the primary process loop to be opened, increasing the risk for contamination.

When sensor maintenance and calibration checks are done at the measuring point, it is hard to decide if the sensor is still performing adequately enough to stay in the process or if it should be replaced. Results between in-line

and lab measurements often differ, and it is difficult for maintenance technicians to know which value is correct.

Sensor calibration and adjustment in the field consumes labor hours and comes with challenges. It can be difficult because of process or weather conditions, and all calibration equipment needs to be present in the field. Paperwork is required for each calibration, which is time-consuming and creates the possibility of data entry errors.

Nevertheless, the performance of analytical sensors is critical to the process and must be checked periodically. Media and buffer solutions used in bioprocesses need to be controlled as they have direct influence on the yield. To maximize the yield in a fermentation process, control of the optimum pH in a narrow range must be accomplished. In many plants, sensors are carefully evaluated, and identical sensors are used throughout the process whenever possible, including in the lab.

In an ideal drug development world, the same sensor could be used at all stages of product development—and the sensor would check its own calibration—thus simplifying calibration procedures, audit paperwork, and scale-up from lab to manufacturing. Such sensors exist today.

Multipurpose Sensors

Two of the most common devices used in the bioprocessing industry are pH and conductivity sensors. Both sensors are subjected to steam-in-place (SIP) and clean-in-place (CIP) procedures in autoclaves, glass fermenters, and batch reactor vessels. It is challenging to protect sensor connections during these processes, and even a small amount of humidity can create unstable values. For these reasons, a pH sensor must be protected against temperature extremes, and undergo regular calibration checks to ensure the pH electrodes are functioning properly.



FIGURE 2. Calibrations are easily done in a laboratory because all the necessary equipment is readily available, and the environment is controlled.



FIGURE 3. Calibrating sensors in a biomanufacturing plant often requires removal of the instrument for calibration in a laboratory setting.

A pH sensor, such as the [Endress+Hauser CPS171D](#) (**Figure 4**), is designed to withstand SIP temperatures of $>121^{\circ}\text{C}$ for 20 minutes, and CIP procedures with NaOH at 85°C .

These types of sensors accompany the active agent during all phases, from development in the lab to large-scale production. Typical applications include:

- Phase separations
- Chromatography
- Fermentations
- CIP monitoring in small pipes
- Ultrafiltration

Industrial pH and conductivity sensors have several features that differ from dedicated lab-only sensors. For example, the [Endress+Hauser CLS82D conductivity sensor](#) has hygienic process connections for installation in pipes or flow vessels, IP68 protection, and is easy to clean, thanks to its electropolished surfaces. The sensor can be sterilized at temperatures as high as 140°C (284°F), and its stainless steel construction (AISI 316L) meets all demands of the pharmaceutical industry.

The entire sensor is EHEDG- and 3A-certified, has FDA conformity, and is available with a certificate of conformity for biopharmaceutical requirements and an inspection certificate for EN 10204-3.1. In short, such a sensor can be used for every step in a drug development process, eliminating the need for sensor changes down the line.

It's All in the Transmitter

As always, a pH or conductivity instrument includes a sensor for measuring the value and a transmitter that converts the sensor's output to a digital value, which then sends it to a control system via a 4–20 mA HART communication protocol, EtherNet/IP, WirelessHART, fieldbus, or any of several other methods. The major difference with



FIGURE 4. The Endress+Hauser CPS171D pH sensor has a glass membrane and reference gel that withstands SIP and CIP procedures.

modern analytical instruments—compared to traditional devices—is that they perform many other functions. For example, the transmitter for a CLS82D conductivity sensor stores measuring system data such as:

- Manufacturer data, including serial number, order code, and date of manufacture
- Calibration data, including calibration date, cell constant, delta cell constant, number of calibrations, and serial number of the transmitter used to perform the last calibration
- Operating data, including temperature and conductivity application ranges, date of initial commissioning, maximum temperature value, and hours of operation at high temperatures

Each instrument supplier provides a similar capability. Sensors with [Endress+Hauser Memosens technology](#) have an integrated electronics unit that stores calibration data and other information. Once the sensor has been connected, the sensor data is transferred automatically to the transmitter and used to calculate the current measured value. The sensor can be calibrated and adjusted independently of the measuring point because calibration data is stored internally. The result is easy calibration in the measuring lab under optimum external conditions, increasing the quality of the calibration. Pre-calibrated sensors can be replaced quickly and easily, resulting in a dramatic increase in the availability of the measuring point. If a sensor has to be removed for calibration, a calibrated sensor can be installed in its place. The new sensor communicates with the transmitter and can be used immediately.

Maintenance intervals can be defined based on stored sensor load and calibration data, making predictive maintenance possible. The transmitter also continuously monitors the sensor, checking for problems and alerting maintenance when the sensor needs cleaning or calibration.

Paperwork for Audits

In addition to the continuous monitoring functionality running in the background, a traceable verification report about the health status of the sensor and instrument can be generated on demand. This report is produced independent of any external devices, directly within the instrument.

For audit-safe documentation purposes, the report can be accessed and downloaded through any asset management system or, if enabled, even wirelessly via a built-in web server. Again, instruments from various manufacturers have auditing capabilities built in. For example, [Endress+Hauser's Memobase Plus](#) with pharma conformity meets FDA 21 CFR Part 11 requirements for an audit trail and password protection, provides traceability for actions and setting changes, and protects sensor and measurement entries, as each action is password protected.

Memobase Plus supports the “as found/as left” requirements in an intelligent and traceable way, stores all values

in a database (**Figure 5**), and provides the audit trail needed for traceability purposes by keeping a chronological account in a table of all the actions and events that have occurred. All changes and actions in Memobase Plus are documented in the audit report with the user's electronic signature and time stamps, thus fulfilling all the record-keeping requirements of the FDA and EMA automatically.



FIGURE 5. Memobase Plus software stores all verification information in a database and produces all the paperwork needed for an audit.

Summary

Today's analytical instruments have built-in capabilities to diagnose problems, perform calibration checks, and generate audit trail reports. Reducing maintenance expenditures by performing fewer calibrations leads to better overall equipment effectiveness, as it increases the availability of the plant. Less downtime for maintenance and fewer unexpected shutdowns improve operations efficiency and operational excellence. Reliable data and certified proof that the measured process value is correct reduces the risk of product quality issues, and therefore supports the goal of maintaining the highest possible level of patient safety.

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