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In the highly regulated biotech and pharmaceutical industries, effective analytical measurement is critical to ensure high production quality and operational efficiency, while meeting hygienic standards. One key measurement application is conductivity analysis in clean-in-place (CIP) processes. Conductivity measurement is so integral to the pharmaceutical manufacturing process that it is easy to take for granted. However, understanding some basics of its operation and correct application can make a big difference in the effectiveness and efficiency of CIP.

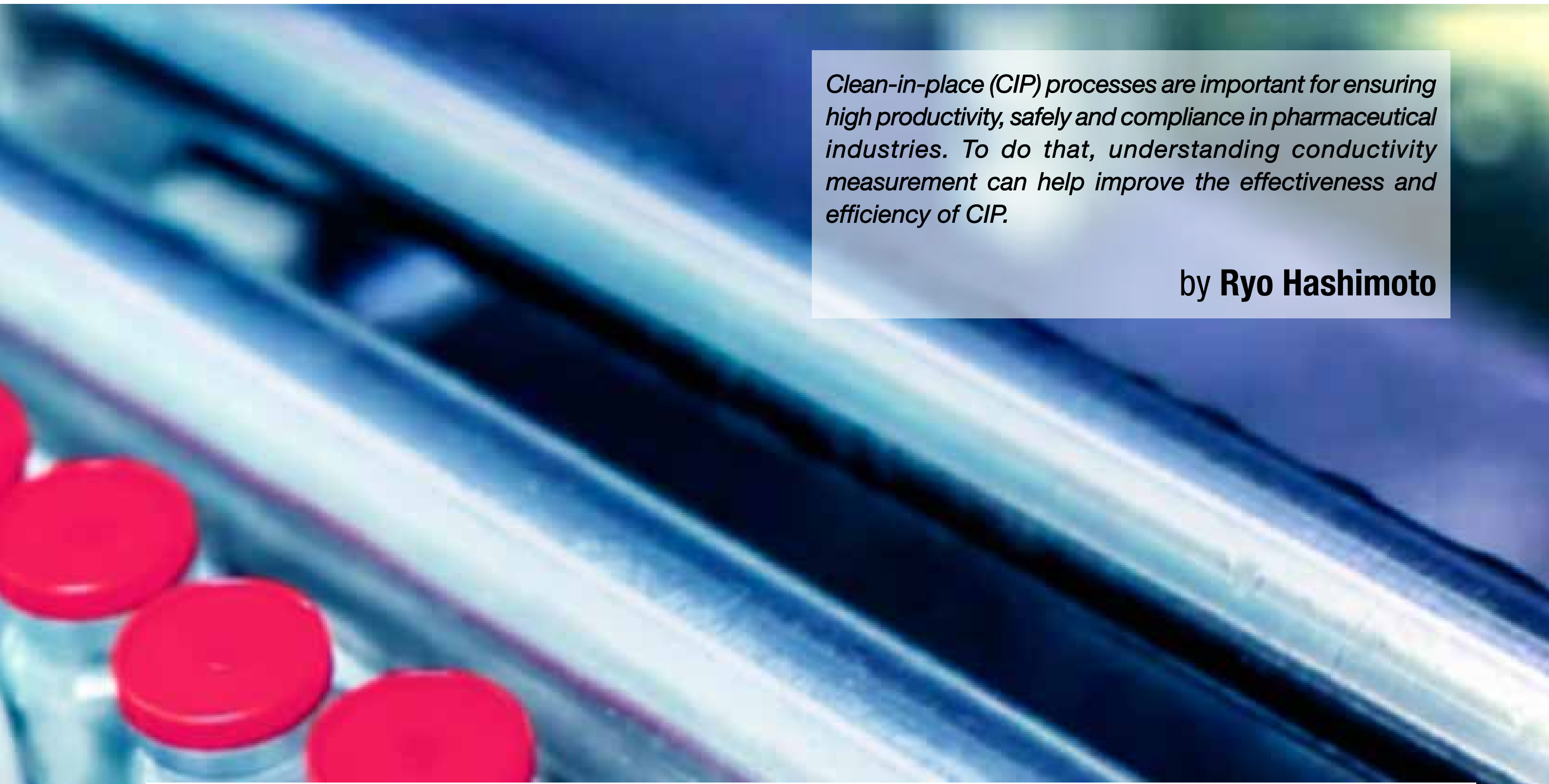
The CIP process ensures that equipment is cleaned and maintained to minimize any possible cross-contamination and improve safety and product quality. Conductivity analysis is a measure of how well a solution conducts electricity. Cleaning solutions are more conductive than water used for flushing the system, so conductivity measurement enables plants to monitor cleaning steps and final rinse to ensure completeness.

Conductivity in CIP

The goals of the CIP process are to maximize safety to prevent any cross-contamination; to speed CIP time and minimize production downtime; and to optimize thermal efficiency to reduce energy requirements by avoiding unnecessary heat loss.

The multi-step CIP process includes initial and final drain, pre-rinse, sodium hydroxide wash, and post-rinse. Some processes may also include a sanitize cycle to reduce bacterial contamination by using strong oxidants such as hydrogen peroxide, ozone, chlorine dioxide, or other chlorine-containing compounds. It is critical that processing plants ensure these chemicals are thoroughly removed to avoid cross-contamination as well as corrosion of equipment.

Effective conductivity analysis in the CIP process for pharmaceutical manufacturing



Clean-in-place (CIP) processes are important for ensuring high productivity, safely and compliance in pharmaceutical industries. To do that, understanding conductivity measurement can help improve the effectiveness and efficiency of CIP.

by **Ryo Hashimoto**

Effective cleaning is determined by detergent strength, cleaning time, and temperature. Conductivity measurement is used throughout the CIP process to ensure the right detergent concentration and monitor the completion of each step. By measuring the conductivity of the returning acid and caustic solutions, plants can confirm that the detergent is the right strength with the correct concentration of acid and caustic for each CIP circuit. These conductivity measurements are proportional to the concentration or solution strength and are recorded for validation. During the CIP process, it is common for fluids to be partially neutralized, so conductivity analysis can indicate when additional concentrate should be added.

By measuring conductivity, plants can determine the interface between cleaning solutions and rinse water. When the conductivity drops to the value of rinse water, it indicates the next step in the cycle can begin. This minimizes CIP time while enabling regulatory compliance. Conductivity is also an effective way to detect the interface between the cleaning solutions and the product, so that valves can be switched at the right time to prevent cross-contamination and product loss.

Measurement of conductivity

To carry a current, a solution must contain charged particles or ions. Most conductivity measurements are made in aqueous solutions and the ions responsible for the conductivity come from electrolytes dissolved in the water. Salts, acids, and bases are all electrolytes. Although water itself is not an electrolyte, it does have a very small amount of conductivity, indicating that at least some ions are present, which in the case of water, are hydrogen and hydroxide. Conductivity is not specific. It measures the total concentration of ions in solution and does not distinguish one electrolyte or ion from another.

Impact of temperature on conductivity

Increasing the temperature of an electrolyte solution increases the conductivity significantly, between 1.5 to 5 per cent per 1°C. To compensate for temperature changes, conductivity readings are often corrected to the value at a reference temperature, typically 25°C. All process conductivity sensors have integral temperature sensors that allow the analyzer to measure the process temperature and correct raw conductivity. Three temperature correction algorithms are commonly used:

- Linear temperature coefficient
- High-purity water or dilute sodium chloride
- Cation conductivity or dilute hydrochloric acid

However, no temperature correction is perfect and unless the composition of the process liquid exactly matches the model used in the correction algorithm, there will be an

Rosemount PUR-Sense conductivity sensor

Rosemount dual channel transmitter

error. Additionally, errors in the temperature measurement itself will result in errors in the corrected conductivity.

The temperature correction algorithm most commonly used in biotech and pharmaceutical CIP processes is the linear temperature coefficient. It is based on the observation that the conductivity of an electrolyte changes by about

$$C_{25} = \frac{C_t}{1 + \alpha(t-25)}$$

the same percentage for every degree Celsius change in temperature. The equation is:

C_{25} is the calculated conductivity at 25°C, C_t is the raw conductivity at t°C, and α is the linear temperature coefficient expressed as a decimal fraction. Although a single temperature coefficient can be used with reasonable accuracy over a range of 30°C to 40°C, accuracy can be improved by calculating a coefficient specifically for

Acids	1.0 – 1.6 percent per °C
Bases	1.8 – 2.2 percent per °C
Salts	1.8 – 3.0 percent per °C

the sample temperature. Approximate ranges for linear temperature coefficients are:

Calibration

Conductivity sensors can either be calibrated against a solution of known conductivity or against a previously calibrated sensor and analyzer. Typically, the sensor should be calibrated at a point near the midpoint of the operating range as calibration changes the cell constant. To calibrate against a standard solution, the sensor is placed in the standard and the analyzer reading is adjusted to match the known conductivity. To eliminate temperature-related errors, it is important to disable temperature compensation and calibrate using the conductivity of the standard at the measurement temperature. Conductivity standards are susceptible to contamination from atmospheric carbon dioxide. Carbon dioxide dissolves in water forming carbonic acid and increasing the conductivity by as much as 1.5 µS/cm. To minimize contamination errors, it is important to avoid using standards with conductivity less than about 150 µS/cm.

To calibrate against a referee sensor and analyzer, let the process liquid flow through the sensors connected in a series and adjust the process reading to match the referee analyzer. Turning off temperature compensation in both analyzers eliminates temperature compensation errors. To ensure the temperature is the same at both sensors, it is important to keep the sample flow high and tubing runs short. Plants should use clean interconnecting tubing to avoid contamination. Because the system is protected from atmospheric contamination, the method is ideal for calibrating sensors used to measure low conductivity samples.

The CIP process is critical for safety, productivity, and compliance, and understanding conductivity measurement, technology, and best practices is key to improving efficiency and effectiveness. APBN

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