Ensure Ultra-Low Residual Hydrogen Peroxide Levels for GMP Pharmaceutical Production

with the Picarro PI2114 Gas Concentration Analyzer

PICARRO

Picarro PI2114 Hydrogen Peroxide Gas Concentration Analyzer

Isolated Aseptic Pharmaceutical Production

High-potency active pharmaceutical ingredient (HPAPI), large-molecule (biologic) drugs, and aseptic fill and finish require isolated, sterile production environments. Vaporized hydrogen peroxide (H_2O_2) is the principal treatment for decontamination in isolated pharmaceutical manufacturing. But if the residual H_2O_2 level is too high after decontamination and aeration, or anytime during the production process, the drug product can oxidize and degrade. At best, this is costly. At worst, it's dangerous.

H_2O_2 Levels for Pharmaceutical Production

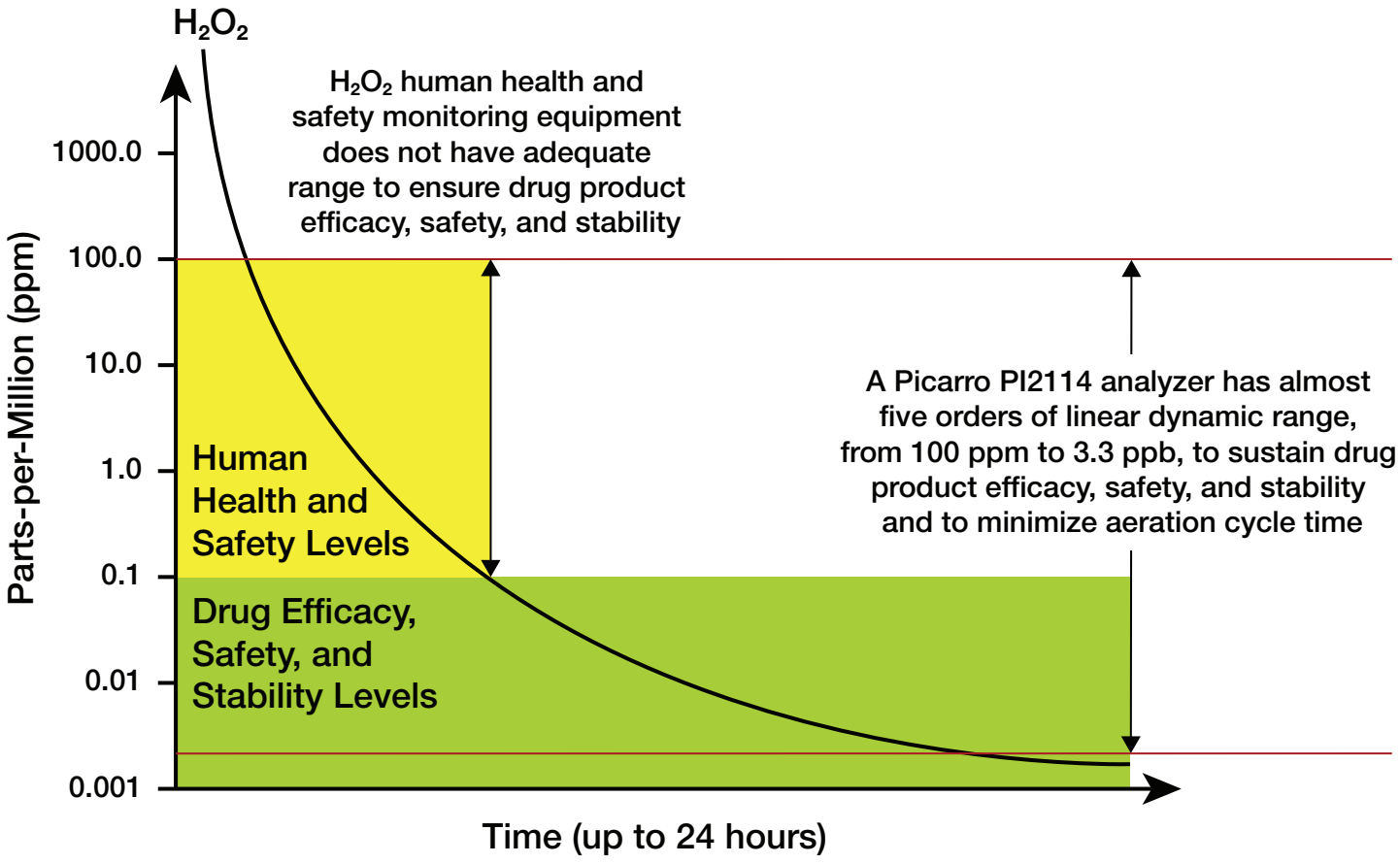
The recommended exposure limit (REL) of H_2O_2 by workers in general industry is 1 part-per-million (ppm), codified in 29 CFR 1900 by the National Institute for Occupational Safety and Health (NIOSH). Other applicable standards my vary based on a specific industry and exposure time, but they are generally in the ppm range. While sufficient for human health and safety, ppm levels are too high to prevent drug oxidation and to sustain efficacy, safety, and stability. The U.S. Food and Drug Administration (FDA) calls for a maximum residual level of 100 parts-per-billion (ppb) in aseptic applications where H_2O_2 is used for sterilization. Some biologic drug producers are setting levels as low as 30 ppb to avoid oxidation. Health and safety monitors that measure exposure limits in ppm cannot ensure H_2O_2 levels are low enough to avoid drug product oxidation.

Ensure Ultra-Low H_2O_2 Levels

As shown in **Figure 1**, the Picarro PI2114 gas concentration analyzer has almost five orders of linear dynamic range, and it can continually measure H_2O_2 levels. This enables users to:

- Measure H_2O_2 levels as low as 3.3 ppb to avoid oxidation and help sustain drug efficacy, safety, and stability.
- Monitor the residual H_2O_2 level from early in the aeration cycle to determine when it is low enough to reliably begin production operations.
- Monitor residual H_2O_2 continually throughout the production process to ensure it does not rise to an unacceptable level due to off-gas contamination.

Figure 1. Monitoring Residual H_2O_2 Levels During the Aeration Cycle



Picarro PI2114 Hydrogen Peroxide Gas Concentration Analyzer

Figure 2. The Picarro PI2114 gas concentration analyzer delivers continuous H_2O_2 measurements from 100 ppm to 3.3 ppb, with 1.1 ppb precision.

Unrivaled Performance with CRDS Technology

The PI2114 analyzer (**Figure 2**) delivers continuous H_2O_2 measurements at 10 second intervals from 100 ppm to 3.3 ppb, with 1.1 ppb precision at 5-minute averaging. Response time is less than 1 minute at 1 ppm from 10% to 90% rise time and 90% to 10% fall time. Patented cavity ring-down spectroscopy (CRDS) technology provides precise, accurate gas concentration measurements over a wide dynamic range because it measures the rate at which the H_2O_2 gas absorbs light.

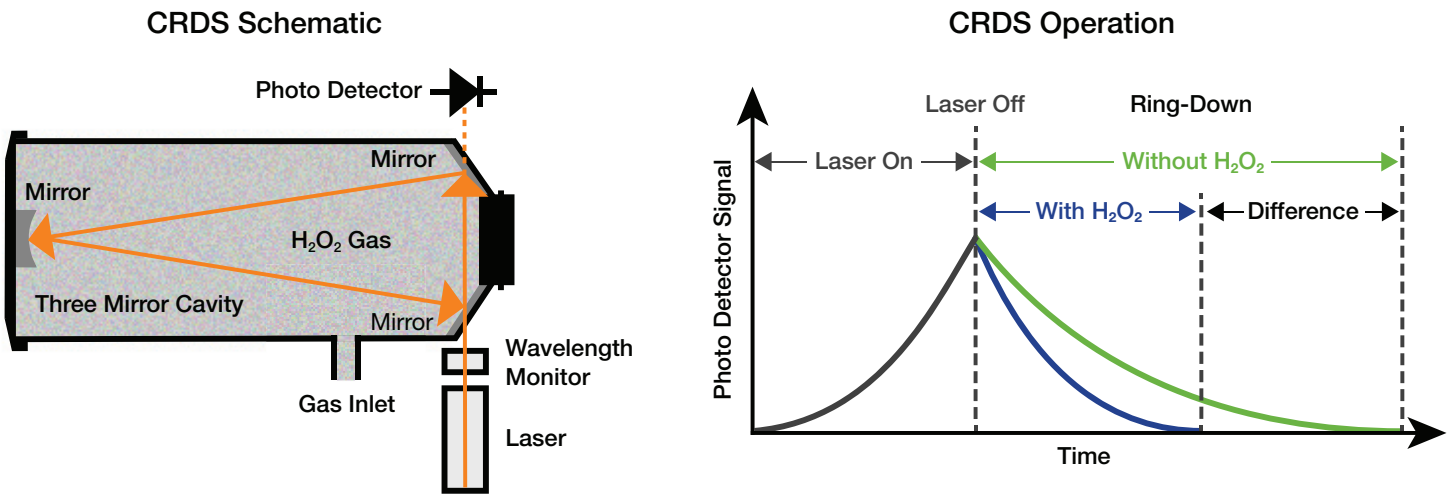
A beam from a single-frequency laser diode enters a three-mirror cavity to create a continuous traveling light wave, as illustrated in the **Figure 3** schematic. The laser is locked to the patented wavelength monitor to ensure spectral precision. When the laser is on, the cavity fills with circulating laser light. A fast photo detector senses a small amount of light leaking through one of the mirrors to produce a signal that is directly proportional to the intensity in the cavity.

When the photo detector signal reaches a threshold level (in a fraction of a microsecond), the continuous wave laser turns off. The light intensity inside the cavity steadily decays to zero in an exponential fashion. This decay, or ring-down, is measured in real-time by the photo detector.

The PI2114 analyzer automatically and continually calculates the ring-down time of the cavity. This produces precise, quantitative measurements. Ring-down measurements are made with and without H_2O_2 in the cavity, and the final concentration data is derived from the difference between the ring-down times, as shown in the **Figure 3** operation illustration.

Therefore, the H_2O_2 concentration measurements are independent of laser intensity fluctuations or absolute laser power. This makes the PI2114 analyzer nearly immune to laser and detector variation. And the long-term stability and patented laser wavelength monitoring technology significantly reduces the need for calibration.

Figure 3. CRDS Schematic and Operation



Picarro PI2114 Hydrogen Peroxide Gas Concentration Analyzer

The Picarro PI2114 analyzer ensures ultra-low residual hydrogen peroxide levels to help avoid oxidation and safeguard drug efficacy, safety, and stability in GMP pharmaceutical manufacturing applications, including high-potency API and biologics manufacturing and aseptic fill and finish (shown).

Pharmaceutical GMP Compliance

The PI2114 analyzer meets GMP requirements for pharmaceutical manufacturing. Software meets 21 CFR Part 11 regulations for electronic records and electronic signatures. This includes defined user roles and access restrictions for administrators, operators, and technicians. And the analyzer can be configured to automatically output measurement data in digital format or through optional analog outputs to a secure SCADA control system or data logging device.

The PI2114 analyzer rarely requires calibration or maintenance. However, GMP guidelines do require that users periodically validate system performance. While Picarro does provide a protocol for validation by H_2O_2 total evaporation, it requires wet chemistry and from 8 to 24 hours to complete.

As an alternative, Picarro has developed a validation protocol that uses methane as a surrogate gas. Compared to the H_2O_2 total evaporation method, the surrogate gas method enables easier and faster validation of the analyzer's accuracy, and includes a report with e-signature capability.

Picarro also provides an installation qualification (IQ) and operation qualification (OQ) check list, so that the analyzer can be installed and put it into operation quickly and easily with GMP compliance.

"Compliance, robustness of processes, and efficiency will need to be squared in one equation."

A report entitled, "*Rapid Growth in Biopharma: Challenges and Opportunities*," by McKinsey & Company discusses critical drug development and production considerations. In regards to meeting quality requirements, the report states that, "Compliance, robustness of processes, and efficiency will need to be squared in one equation." The Picarro PI2114 analyzer is designed to help companies address all three challenges simultaneously to ensure ultra-low levels of residual H_2O_2 in GMP pharmaceutical production environments.

About Picarro

Picarro is a leading provider of gas concentration and isotope analyzers, with over 3,000 instruments across 62 countries. Major pharmaceutical, CMO, and isolator companies have used Picarro hydrogen peroxide analyzers for over a decade. Picarro analyzers and systems are used in a wide range of other applications, including energy, utilities, semiconductor, and geosciences. Our PhD scientists and optical engineers design and produce instruments in our headquarters located in the heart of Silicon Valley, California.

3105 Patrick Henry Drive, Santa Clara, CA 95054 | 408-962-3900 | sales@picarro.com | picarro.com

PICARRO

LIT CODE: PI2114-BR03-V1.0-190221