The pharmaceutical industry uses ozone (O₃) as a means to create pharmaceutical-grade water, which is used for both cleaning equipment and manufacturing products. Adding ozone to water serves as a microbial disinfectant, and when it is dissolved in water ozone reacts with bacteria, viruses and other microorganisms to create removable solids of dissolved minerals and neutralise certain chemicals. Ozone can also break down pesticides and remove unwanted colour. It leaves no taste, odour and – most importantly for the pharmaceutical industry – no dangerous chemical residues. Ozone also has a very high oxidation potential and works quickly, enabling pharmaceutical manufacturers to reduce downtime and increase productivity.

According to US Pharmacopoeia regulations (1), pharmaceutical-grade water must be validated to demonstrate that it meets certain requirements for ionic and organic chemical purity, and must be protected from microbial contamination. Monitoring the levels of dissolved ozone in pharmaceutical-grade water is a high priority, as the ozone measurement is used as an indicator that disinfection has taken place and no residual dissolved ozone is in the water. As such, pharmaceutical manufacturers must measure the levels of dissolved ozone at various points in the process to ensure that adequate ozone concentrations are present during sanitation, and that there is no residual ozone at the point of use. Because the use of high-quality water is essential to nearly all aspects of the pharmaceutical manufacturing process, the industry needs reliable water quality-monitoring techniques.

**OZONE AS A DISINFECTANT**

Ozone is the strongest standalone oxidiser currently available for water treatment. By using ozone as a disinfectant, pharmaceutical manufacturers can avoid the drawbacks of the traditional method of chlorination to purify water; these include residual chlorine compounds, slower speeds and the inability to destroy Cryptosporidium, a one-celled parasite that can cause the gastrointestinal illness cryptosporidiosis. Ozone's advantages over chlorine as a disinfectant also include its: easy removal; capacity to reduce total organic carbon (TOC) levels; ability to oxidise inorganic materials such as nitrates and sulphides; and capability as a clarifier.

During the pharmaceutical manufacturing process, ozone is used to treat pharmaceutical-grade water as well as water for injection (WFI), ensuring that the water distribution network is sanitary. As the ozone-injected water is flushed through the distribution system, disinfection is extremely effective compared to conventional steam-cleaning solutions.
Ozone monitoring enables the pharmaceutical industry to achieve regulatory compliance with standards for pharmaceutical-grade water. To measure the ozone level, the residual ozone quantity is multiplied by the time the ozone is in contact with the water. A direct dissolved measurement of ozone can then be linked to disinfection efficacy.

TRADITIONAL MONITORING METHODS
By measuring dissolved ozone levels, manufacturers can validate their process for disinfecting water and ensure that no residual ozone is present after disinfection is complete. Dissolved ozone has traditionally been monitored and controlled using redox analysers, ultraviolet (UV) spectrophotometers, amperometric or potentiometric electrochemical monitors, colorimeters and sensors that measure the photochemical reaction of ozone with ethylene.

However, these instruments can demonstrate significant shortcomings, which have made validating these methods difficult. Redox analysers are nonlinear and not sensitive enough to accommodate certain applications. UV spectrophotometers are expensive and complicated to use, requiring a reference gas and moving parts in the form of solenoid valves as well as incorporating optics that may easily become misaligned. Additionally, the UV spectrum of ozone may be confused with that of other compounds present in the water sample being monitored. The use of amperometric or potentiometric electrochemical monitors can also be problematic when monitoring ozone, as these instruments are not ozone-specific; they also produce a very small signal in low-conductivity water and are not efficient in ultra pure water. Such sensors have proved unreliable and inaccurate as electrodes and membranes are easily fouled, internal solutions may become contaminated and maintenance requires complex disassembly. The use of colourimeters does not offer continuous sample analysis and requires the disposal of contaminated samples. The photochemical approach is also becoming less common due to the need for a continuous supply of reagents and the ability to handle exhaust products.

EMERGING TECHNOLOGIES
Pharmaceutical manufacturing is a highly competitive business, and manufacturers require a fast, cost-effective and online method of monitoring ozone in water systems. One emerging technology is a dissolved ozone monitor that can offer continuous online monitoring and control of ozone systems. This instrument incorporates a dissolved ozone sensor installed in a flow cell. The sample is piped to the flow cell using 1/4" internal diameter (id) sample tubing. The standard flow cell arrangement uses a constant-head overflow system to ensure stable flow and pressure across the sensor, regardless of sample line pressure and flow fluctuations. A low-volume flow cell is used for installations where minimum sample flow is desired. In these applications, special attention has to be paid to the control of flow and pressure across the sensor membrane.

The instrument uses a highly selective, membrane-covered polarographic sensor that does not require the addition of chemical reagents. Dissolved ozone readings are easily achieved without measurement interference from other sample components such as residual chlorine. The need for maintenance is greatly reduced as the technology does not require the use of moving parts, meaning that there are no tubing breaks or pumps and motors that can burn out.

The technology has been designed with the flexibility to enable optional dual measurement capability and provides both dissolved ozone and pH analogue outputs. Dual analogue outputs can also be configured to track ozone and temperature, ozone and ozone, or ozone and pH for increased process control.

A standard feature of this alternative technology is a proportional-integral-derivative (PID) control function that can be configured quickly and easily. To use this function, the primary 4-20 mA output must be assigned for PID control. While not suitable for systems with rapid flow-changes requiring compound-loop control, the PID function can handle many stable flow applications.

This technology has been proven to meet a variety of monitoring applications and is capable of measuring dissolved ozone concentrations as low as 0-200 parts-per-billion (ppb) full scale down to 5 ppb. While providing...
the sensitivity needed for demanding applications such as pharmaceutical-grade water or semiconductor wash water, this technique can also easily accommodate high-range applications requiring 0-20 or 0-200 parts-per-million (ppm).

CALIBRATION REQUIREMENTS
Pharmaceutical manufacturers must implement a reliable and accurate calibration procedure for dissolved ozone monitors in order to ensure the precision of data derived from the instrument. Even after initial installation of the monitoring system, the calibration of ozone monitors should be checked on a monthly basis at least. Pharmaceutical companies require efficient calibration systems to meet the strict regulatory requirements specified by the European and the US Pharmacopoeias, which regulate the quality of purified water and WFI in the manufacture of pharmaceutical products. Additionally, the European Pharmacopoeia requires that water monitoring systems be regularly calibrated against one or more suitable certified standard solutions. For example, for conductivity monitoring, calibration should achieve accuracy within three per cent of the measured conductivity.

Preparing an analytical standard of ozone with which to calibrate the instrument is not possible due to the instability of aqueous ozone solutions. The only calibration method recognised by the International Ozone Association and the US Environmental Protection Agency (EPA) is Method 4500 Indigo Dye (2). It is also the only traceable method of calibration. All other calibration methods – such as air calibration using relative diffusion coefficients of oxygen and ozone – should cross-reference Method 4500.

This method is referred to as a ‘bleaching chemistry’ because the colour developed on the ozone sample is lighter than a reagent blank run on ozone-free water. As ozone reacts quantitatively with the blue indigo dye, the colour of the solution fades. Colour intensity is then measured with a photometer (either a colourimeter or a spectrophotometer) in order to determine the amount of ozone present.

To calibrate a dissolved ozone monitor, a photometer measures the dissolved ozone level in a sample. The photometer should be calibrated using the US National Institute of Standards and Technology (NIST) traceable secondary standards every year. Before each calibration, the photometer can be verified using the same secondary standards. To maximise the accuracy of the calibration, a dissolved ozone concentration of at least 50 to 100 ppb is used when calibrating the monitor. The calibration should be carried out when the ozone concentration in the water is steady. Three samples are taken and an average is calculated.

CONCLUSION
Pharmaceutical manufacturing facilities rely on quick access to high-quality water throughout the manufacturing process. The use of ozone for water purification offers many benefits for pharmaceutical manufacturers, specifically regarding its capabilities as a disinfectant and purifier. With regulations becoming even stricter with regard to the ionic and organic chemical purity, and microbial decontamination of pharmaceutical-grade water, there is a strong need for reliable water quality-monitoring technologies in the industry. Monitoring the levels of dissolved ozone in pharmaceutical-grade water provides manufacturers with needed traceability to satisfy regulatory agencies.

Traditional dissolved ozone monitoring methods lack sensitivity and can be expensive, complicated to use and inefficient. Dissolved ozone monitors are an emerging technology that offers the benefits of a fast, relatively inexpensive and online method of monitoring ozone in water systems with reliable results. The instrumentation does not require the addition of chemical reagents and can easily achieve readings without measurement interference from other sample components such as residual chlorine. Manufacturers also benefit from reduced maintenance costs and the flexibility of optional dual measurement capability. Maintaining a stable zero point, these innovative methods achieve the highest levels of calibration accuracy, ensuring reliable and accurate results in this highly regulated industry. The pharmaceutical industry can also reap further benefits from this emerging technology through reduced downtime and lower costs.

References