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⟨415⟩ MEDICAL GASES ASSAY

INTRODUCTION

The evaluation of the purity of a gas used for medical treatment or as a component of a pharmaceutical process is the purpose of a *USP* medical gas monograph. The purity generally is evaluated by an assay for the content of the article and by analyses for trace impurities. The application of gas chromatography, paramagnetic analysis, and detector tubes to medical gases is somewhat different from traditional procedures used for analytes in the liquid phase and therefore warrants a separate description. This general test chapter focuses on the assay for content tests. Sampling for impurities is addressed in general chapter *Impurities Testing in Medical Gases* ⟨413⟩.

This chapter includes sampling and qualification aspects of gas chromatographic and paramagnetic analyses of medical gases. In addition, it includes a description of the initial set-up, validation, and calibration of these instruments. The specific assay procedures are defined in the specific monograph for that gas.

The basic definitions of instrumental qualification and validation are included in general information chapters *Analytical Instrument Qualification* ⟨1058⟩ and *Validation of Compendial Procedures* ⟨1225⟩, respectively, and will not be repeated. However, when variations of the materials presented in these chapters are necessary due to the character of the analyte, this chapter will define those variations.

METHODS

Gas Chromatography (GC)

See *Chromatography* ⟨621⟩.

Detectors for Medical Gases Assay

The two most common detectors used in the analyses of medical gases are the thermal conductivity detector (TCD) and flame ionization detector (FID).

The TCD will detect any gas or vapor that has a thermal conductivity (TC) that differs significantly from the high TC of the reference gas, usually helium, therefore it is virtually universal. However, the generally accepted lower detection limit for the TCD is 50 ppm v/v. This represents a limitation for the evaluation of trace impurities in medical gases.

The FID is also used for the evaluation of trace impurities in medical gases, because it is more sensitive to organic compounds but does not produce a signal for most common medical gases.

QUALIFICATION

Installation Qualification (IQ)

The IQ requirements ensure the gas chromatograph hardware and software (or readout device) is installed safely and in accordance with the GC manufacturer's instructions.

Consideration should be given to the following as applicable:

- Suitability of the sample system (including connections);
- Leakage (should be leak free);
- Representative sampling;
- Sample flow rates;
- Response time;
- Correct output signals;
- Power supply (including voltage regulation); and
- Appropriate environmental conditions of the instrument and of the sample itself (e.g., temperature and pressure).

Operational Qualification (OQ)

OQ verifies that the GC performs as intended within its anticipated operating range. For medical gas final product testing, the GC is tested to ensure repeatability (verification that relative standard deviation is consistent with claims) for each analyte of interest. Due to the specific nature of medical gas testing and the limited number of analytes, routine calibration and periodic calibration verification of a GC instrument and the testing procedure may be used in place of initial or periodic OQ. When an instrument is used for a broader range of analytes, the replacement of OQ with calibration and periodic calibration verification is inappropriate.

Performance Qualification (PQ)

For medical gas final product testing, the GC is periodically checked at appropriate intervals during analytical runs with a calibration gas (i.e., verifying that the results are consistent with a named concentration within acceptable accuracy and precision ranges after a specific number of sample injections).

Paramagnetic Oxygen Measurement

THEORY

The paramagnetic analyzer measures the displacement of a diamagnetic gas (nitrogen) by a paramagnetic gas (oxygen), in a strong magnetic field. A measuring cell typically employs a glass dumbbell with nitrogen-filled spheres that is suspended on a torsion strip between magnets that concentrate the flux around the dumbbell. When oxygen molecules enter the measuring cell, the dumbbell is deflected by the force exerted by the oxygen molecules that are attracted to the strongest part of the magnetic field. By using optical sensors, a feedback coil, and suitable electronics, analysts measure an output that is directly proportional to the partial pressure of oxygen.

Oxygen is the only paramagnetic gas present above trace levels in the atmosphere. However, paramagnetic analyzers can be affected by the magnetic susceptibility of the background gas. Therefore changes to background gases in *USP* monographs should be avoided.

Design Considerations

The design considerations for the purchase of new instruments may include the following parameters.

DRIFT

A change of the output of the instrument for a given concentration over a stated period of time under constant conditions and without any adjustments being made to the instrument by external means. Drift is the summation of two components, zero drift and span drift. Drift determines the frequency of instrument calibration.

ZERO DRIFT

A change in the output when zero gas is being measured.

SPAN DRIFT

A change in the output at the level of oxygen concentration that is being measured.

OPERATING TEMPERATURE

The ambient temperature range for which the stated performance specification of the instrument will remain valid. A larger temperature coefficient will indicate that a smaller change in ambient temperature is permitted before re-calibration is required.

OPERATING PRESSURE

The instrument should operate at the inlet pressures of the samples to be tested.

Qualification Aspects

INSTALLATION QUALIFICATION (IQ)

The IQ requirements ensure the oxygen analyzer hardware and software (or readout device) is installed safely and in accordance with the oxygen analyzer manufacturer's instructions.

Consideration should be given to the following as applicable:

- Suitability of the sample system (including connections);
- Leakage (should be leak free);
- Representative sampling;
- Sample flow rates;
- Response time;
- Correct output signals;
- Power supply (including voltage regulation); and
- Appropriate environmental conditions of the instrument and of the sample itself (e.g., temperature and pressure).

OPERATIONAL QUALIFICATION (OQ)

The OQ requirements verify that the paramagnetic analyzer performs as intended within its anticipated operating range and is suitable for the actual conditions of use. Instruments and apparatus should be calibrated and used in accordance with the oxygen analyzer manufacturer's instructions. Because of the specific nature of the instrument, routine calibration may be used in place of initial or periodic OQ testing.

PERFORMANCE QUALIFICATION (PQ)

The PQ requirements verify that the paramagnetic analyzer performs as intended in its normal operating environment. For medical gas final product testing, the paramagnetic analyzer is initially calibrated (zeroed and spanned using a certified standard) in accordance with the oxygen analyzer manufacturer's instructions and is periodically recalibrated to ensure continued acceptable performance.

ZEROING THE INSTRUMENT (ESTABLISHING THE LOWER LIMIT)

Using the certified standard defined in the monograph, establish a zero setting on the analyzer by passing the zero gas into the analyzer at the oxygen analyzer manufacturer's suggested flow rate. Maintain the flow until a stable reading is observed on the instrument. As necessary, adjust the zero setting to a value of 0.0% according to the oxygen analyzer manufacturer's instructions. Confirm the reading is stable.

[NOTE—Depending on the intended use of the instrument, zeroing to a setting other than 0.0% is an acceptable alternative to this procedure if it provides greater measurement precision.]

SPANNING THE RANGE OF USE

Establish the upper limit (span) with a span gas defined in the monograph and appropriate for the range of use. Pass the span gas through the instrument at the manufacturer's suggested flow rate. Confirm the reading is stable. Adjust the span setting to the certified value of the reference standard according to the oxygen analyzer manufacturer's instructions. Confirm the reading is stable.

VALIDATION

Validation of this instrument is generally completed during the (IQ/OQ) process. Routine verification is performed as described in the OQ/PQ sections of this chapter; and, therefore, specific information on instrument validation is unnecessary.

PROCEDURE

For Off-line Instrument

Before analysis, the instrument is calibrated by zeroing and spanning as described in the PQ section.

[NOTE—The calibration need not be run concomitantly with the test samples.]

Connect the sample gas to the instrument, and establish a constant flow into the analyzer at the analyzer manufacturer's suggested flow rate. Maintain the flow until a constant reading is observed on the instrument. The definition of a constant reading is included in the analyzer manufacturer's instructions or in the user's instrument qualification documentation.

For On-line Instrument

The calibration intervals are defined by the analyzer manufacturer, by past history, or by statistical means. Establish a constant flow into the analyzer at the manufacturer's suggested flow rate.

SAMPLING

Sampling from Liquid Phase

Cylinders containing a dip tube allow a liquid sample to be obtained from the valve outlet with the cylinder in the upright position. If a dip tube is not present, the cylinder should be placed in an inverted position with the cylinder and main valve safely supported (so the liquid phase is in contact with the valve).

Sampling of medical gases should always be conducted using the required regulator. Regulators should be purged with the gas that will be sampled. When necessary, the flow to the analyzer should be measured using a calibrated flow-measuring device.

Sampling from Gaseous Phase

Cylinders that do not contain a dip tube allow a gaseous sample to be obtained from the valve outlet with the cylinder in the upright position. If a dip tube is present, the cylinder should be in an inverted position with the cylinder and main valve safely supported (so the gaseous phase is in contact with the end of the dip tube). Sampling of medical gases should always be conducted using the required regulator.

CERTIFIED STANDARDS FOR MEDICAL GAS ANALYSIS

USP monographs for medical gases require tests that use certified standards for instrument calibration and analytical determinations. Such compendial testing may be conducted using reference materials that are traceable to the U.S. National Institute of Standards and Technology or other National standards-setting organizations, e.g., Institute for National Measurement Standards (Canada). The individual monographs and the reagents, indicators, and solutions section refer to the nominal percent of various certified standards required to perform medical gas analysis. The requirements for the actual certified concentrations in terms of variance from the nominal value are indicated in the *Reagents, Indicators, and Solutions* section for each respective certified standard.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
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