B&R Compliance Associates LLC

Regulatory Update Bulletin

Bulletin Number

BR13-002

USP Proposes Changes for Medical Gases

Proposed Monograph Changes

BRIEFING

Oxygen, *USP 35* page 4179. The revision proposal published in *PF* 35(4) page 861 is canceled and replaced with the following proposal.

1. Replace *Identification* test *A* with a specific, selective, and positive identification test based on the paramagnetic signal due to the presence of oxygen.
2. Replace *Identification* test *B* with *Acceptance criteria* agreement in the *Assay* to ensure that the article complies with both identification and strength.
3. Revise the *Assay* to use the specific and selective paramagnetic oxygen measurement technique that is described in the general chapter *Medical Gases Assay* ⟨415⟩.
4. Revise the *Impurities* section to include a reference to the general chapter *Impurities Testing in Medical Gases* ⟨413⟩. Also revise the specific tests to be consistent with the general chapter.
5. Revise the *Packaging and Storage* section to be consistent with gas manufacturers' storage practices.
6. Revise the *Labeling* section to be consistent with the proposed *Packaging and Storage* section revision.
7. Delete the test for *Odor* to be consistent with the *USP* monograph modernization initiative, because the test presents a safety concern. According to *General Notices 8.120, Odor*, “An odor designation is descriptive only and should not be regarded as a standard of purity for a particular lot of an article.“ The

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monograph contains sufficient tests to ensure identity, quality, and purity of the material.

Medical Air, *USP 35* page 2080. The revision proposal published on page 828 of *PF* 35(4) [July Aug. 2009] is canceled and replaced with the following proposals:

1. Introduce *Identification* test *A* based on the paramagnetic signal due to the presence of oxygen in *Medical Air*.
2. Introduce *Identification* test *B* based on the *Assay* acceptance criterion agreement to ensure that the article complies with strength.
3. Revise the *Assay* to use the specific and selective paramagnetic oxygen measurement technique, which is described in the general chapter *Medical Gases Assay* ⟨ 415 ⟩.
4. Revise the *Impurities* section to include reference to the general chapter *Impurities Testing in Medical Gases* ⟨ 413 ⟩. Also, revise the specific tests to be consistent with the general chapter.
5. Revise the *Packaging and Storage* section to be consistent with gas manufacturers' storage practices.
6. The *Labeling* section has been revised to include the way Medical Air is manufactured to assess the necessity for impurities testing based on the manufacturing process.
7. Delete the test for *Odor* to be consistent with the *USP* monograph modernization initiative, because it presents a safety concern. According to *General Notices 8.120, Odor*, "An odor designation is descriptive only and should not be regarded as a standard of purity for a particular lot of an article." There are

sufficient tests in the monographs to ensure identity, quality, and purity of the material.

Proposed Standard Changes

BRIEFING

Oxygen Certified Standard. The proposal for this new reagent published on page 1339 of *PF* 35(5) [Sept.–Oct. 2009] is canceled and replaced with this revised proposal. This reagent is used in the *Assay* of the monograph for *Oxygen*, which appears elsewhere in this issue of *PF*.

Add the following:

Oxygen Certified Standard—A suitable NLT 99.99% oxygen certified standard is available from most suppliers of specialty gases.

Nitrogen Certified Standard. The proposal for this new reagent published on page 990 of *PF* 35(4) [July–Aug. 2009], in *Reagents, Indicators, and Solutions*, is canceled and replaced with this revised proposal. This reagent is used in the *Assays* of the monographs for *Medical Air*, *Oxygen*, and *Oxygen 93 Percent*, which appear elsewhere in this issue of *PF*.

Add the following:

Nitrogen Certified Standard—A suitable NLT 99.99% nitrogen certified standard is available from most suppliers of specialty gases.

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Proposed New General Chapters

BRIEFING

〈413〉 **Impurities Testing in Medical Gases.** This new general test chapter is being developed to support the medical gases monographs. The chapter outlines the gas sampling procedure from high-pressure containers specifically for determining impurities using various detector tubes.

(AER: K. Zaidi.) RTS—C64174

Add the following:

■〈413〉 **Impurities Testing in Medical Gases**

INTRODUCTION

This general test chapter defines the safe and proper means to sample high-pressure gas containers of different medical gas compositions using the manufacturer's suggested total gas volume for the purpose of conducting detector tube analysis to satisfy the *USP* monographs. See *Reagents* in the section *Reagents, Indicators, and Solutions* for information on each referenced detector tube.

There are two types of detector tubes currently manufactured, those to be used with a manual hand pump of fixed volume (e.g., 100 mL/pump stroke), and those used in a continuous flow system that can be set to pass a volume of gas through the detector tube at approximately one (1) atmosphere. It is important to match the appropriate detector tube type to the mode of gas volume exchange.

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To ensure that the required gas volume has passed through the detector tube, measure the gas volume at the time of the analysis either by using a hand pump or using a flowmeter that is calibrated to the subject gas or corrected via a calibration chart. Flowmeter manufacturers generally provide a chart of the gas volume flow of common gases for each of the flow tubes identified in this general chapter. [NOTE—See general chapter *Medical Gases Assay* ⟨415⟩ for sampling.]

Continous Flow System

Identify the gas contained in the container and select the appropriate gas regulator. Secure the regulator to the gas container. Do not apply lubricant or Teflon tape to the container-to-regulator connections. Purge the regulator with the gas under test. Select float setting to achieve total gas volume as recommended by the manufacturer. Attach the detector tube, then adjust the flow rate to the required level as indicated by the charts that accompany the flowmeter and the detector tube. Time the gas flow to achieve the desired total gas volume ±10 s. At the allotted time close the regulator valve, then the main container valve. Observe the tube while it is still attached to determine the degree of color change and record the result. Remove the tube, and disconnect the apparatus, vent the regulator gas pressure to atmosphere, and remove the regulator from the container. Dispose of the tube after use.

Hand Pump—Fixed Volume

The alternative approach is to apply the gas detector hand pump. The system draws a

consistent volume with each pump stroke. To ensure the accuracy of the total gas volume, the user must follow the manufacturer's suggested recommendation about how to pump.

《415》 **Medical Gases Assay.** This new general test chapter is being developed to support the medical gases monographs. The chapter includes information on sampling and qualification for conducting medical gases assay testing using gas chromatography and paramagnetic analyzers. It also covers validation and calibration of these instruments.

(AER: K. Zaidi.) RTS—C64173

Add the following:

■《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》.

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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 Methods* ⟨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 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 challenge testing of a GC instrument and the testing procedure may be used in place of initial or periodic OQ.

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When an instrument is used for a broader range of analytes, the replacement of OQ with calibration and challenge testing 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.

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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 being measured.

Span Drift—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 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;

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- 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 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 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 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 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 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 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 manufacturer's instructions or in the user's instrument qualification documentation.

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

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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.

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USP/NF Revision Timeline

- Public comment period ends March 31, 2013
- The earliest targeted official publication would be in USP 36-NF 31, second supplement
  - Release Date – June 2013
  - Official Date – December 1, 2013

B& R Compliance will continue to monitor these changes and provide further updates as appropriate.

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