Is A Certificate Of Analysis (CoA) Required For All Incoming Bulk Medical Gas Deliveries?

Executive Summary

The short answer is, “No.” However, if you do not have a CoA for incoming bulk medical gas deliveries, you must perform full USP/NF testing on the bulk tank after delivery. This testing is easy for Liquid Oxygen, USP and Liquid Nitrogen, NF. Details below…

FDA Regulations

The FDA regulations for this activity are contained in 21 CFR 211 Subpart E. See the excerpts below. The full text of the regulation is in Appendix A. (Bolding added for emphasis.)

> **Subpart E -- Control of Components and Drug Product Containers and Closures**
>
> Sec. 211.80 General requirements.
> (a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed….
>
> Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures….
> (d) Samples shall be examined and tested as follows:
> (1) At least **one test** shall be conducted to **verify the identity** of each component of a drug product. Specific identity tests, if they exist, shall be used.
> (2) Each component shall be **tested for conformity with all appropriate written specifications for purity, strength, and quality**. **In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier`s analyses through appropriate validation of the supplier`s test results at appropriate intervals**….

Draft Guidance

In 2003, the FDA published their latest thinking on compliance for medical gas manufacturers, “Current Good Manufacturing Practice for Medical Gases - DRAFT GUIDANCE”. (Bolding added for emphasis.)

> H. Liquid Supply (Certificate of Analysis (COA))
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> The medical gas industry routinely relies on COAs to reduce the amount of finished product testing performed. For example, if a COA lists all of the impurities tested for by a supplier, then it would be unnecessary for a manufacturer to perform a test for the listed impurities on the finished drug product. **If no COA is received, the Agency recommends that the finished drug product testing include all impurities listed in the USP monograph or established specifications for each medical gas.**

In addition, the COA for medical oxygen usually contains **the air liquefaction statement** as required by the USP, and as a result, it would be unnecessary for a manufacturer to test for carbon dioxide and carbon monoxide impurities. If a manufacturer does not maintain the air liquefaction statement for its medical oxygen, the Agency recommends that the manufacturer perform testing for carbon dioxide and carbon monoxide impurities.

…If a company relies on a COA to reduce the amount of testing required by the USP, we recommend the company establish the reliability of the supplier's analysis at appropriate intervals. This can be accomplished by the manufacturer, by a third party, or by a contract-testing laboratory.

Summary

If you ***do not*** receive a CoA from your supplier, you must conduct full USP/NF testing on the incoming bulk delivery:

Oxygen – Full USP Testing

Test	Specification	Method
Assay (Purity)	> 99 %	Typically using a validated Servomex
Identity	Positive	Typically using a validated Servomex
Odor	None	Organoleptic (sniff test)

Nitrogen – Full NF Testing

Test	Specification	Method
Assay (Purity)	> 99 %	GC or validated Servomex, etc.
Identity	Positive	Burning splint (as of April 2010)
Odor	None	Organoleptic (sniff test)
Carbon Monoxide	<10 ppm	Detector Tube

If you ***do*** receive a CoA from your supplier, you must conduct at least one identity test on the incoming bulk delivery:

Oxygen – Minimum Identity Testing

Test	Specification	Method
Identity	Positive	Typically using a validated Servomex

Nitrogen – Full NF Testing

Test	Specification	Method
Identity	Positive	Burning splint (as of April 2010)

In addition, you must verify the validity of the suppliers' analysis. This should be conducted annually and can be done by you or another lab.

Recommendations

1. If your supplier provides a CoA at no charge with each incoming bulk delivery of oxygen and nitrogen, then accept the CoA and file it with your incoming analysis records. Conduct full USP/NF testing anyway… because it is so simple to do.
2. If your supplier charges for the CoA, refuse to pay for the CoA. Conduct full USP/NF testing … because you are required to do so without a CoA.

3. Be sure the “Produced by air liquefaction” statement appears on the delivery paperwork for liquid oxygen. This statement makes it possible to avoid testing the liquid oxygen for carbon dioxide and carbon monoxide impurities.
4. If you are receiving other bulk drugs (CO_2, N_2O, He), follow the concepts listed above and your SOPs for your incoming bulk delivery testing.

Appendix A – Full Text of 21 CFR 211, Subpart E, Control of Components

Subpart E -- Control of Components and Drug Product Containers and Closures

Sec. 211.80 General requirements.
(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Sec. 211.82 Receipt and storage of untested components, drug product containers, and closures.
(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of § 211.80.

Sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures.
(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier`s analyses through appropriate validation of the supplier`s test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier`s test results through appropriate validation of the supplier`s test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

Sec. 211.86 Use of approved components, drug product containers, and closures.
Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

Sec. 211.87 Retesting of approved components, drug product containers, and closures.
Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with § 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

Sec. 211.89 Rejected components, drug product containers, and closures.
Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Sec. 211.94 Drug product containers and closures.
(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.