

NOTICE

On July 14, 2000, the NWSA and CGA jointly submitted a petition to the FDA to stop “Fresh Air” distribution in any form. You may read the entire petition and supporting documents at the NWSA website at:

<http://www.nwsa.com/secure/safetypetitiondir.htm>.

Although the NWSA does not endorse “Fresh Air” and some of its provisions, we realize that it is still recognized by the FDA as “an overview of cGMP information.” Therefore, the NWSA will continue to make “Fresh Air” available to its members until the FDA rules on the petition.

“[Fresh Air] contains an overview of cGMP information, as it would apply to the medical gas industry and is not a regulatory requirement.” -- FDA Memorandum, April 27, 2000

FRESH AIR '2000' [Reformatted from original]

A LOOK AT FDA'S MEDICAL GAS REQUIREMENTS

Fresh Air '2000' provides FDA's interpretation of how the minimum current good manufacturing practice (CGMPs) regulations apply to the manufacturing, filling, transfilling, cascading, etc. of medical gases, both compressed and cryogenic. Please note this presentation is not all-inclusive.

The information contained in this document is based on FDA's inspecting approximately 800 locations each year and from industry input from organizations such as the Compressed Gas Association, National Welding Supply Association, and National Association of Medical Equipment Suppliers, etc.

Medical gases are prescription drugs that must be dispensed by prescription only. Each firm has a responsibility to determine if its consignee, not the patient is authorized to purchase the drug gas, and if required, is registered with FDA, and properly licensed with the state, where required prior to selling them medical gas.

Medical gases not filled in accordance with the current good manufacturing practice regulations can and have resulted in medical gases that are contaminated which can cause serious injury and/or death to patients who were administered the gas. In fact, injury and death of patients has occurred in the past due to CGMP problems.

Who is required to register? Any individual or firm filling cylinders or liquid containers (via liquid to liquid, liquid to gas, gas to gas) is considered a manufacturer and as such is required to register and list with the agency and to comply with the CGMPs. In addition, a firm should check with its state to determine if there are any state requirements, such as licensing.

Any pharmacy involved in the manufacturing or filling of medical gases for patient use outside of that facility would be required to register and list with the agency, to comply with the CGMPs, and will be inspected. However, a hospital pharmacy that fills and provides oxygen for inpatient use only, would not be required to register.

Presented by Duane Sylvia, Consumer Safety Officer, Center for Drug Evaluation and Research, Office of Compliance during the CDER Medical Gas CGMP Workshop held on March 15, 2000, at Rockville, Maryland.

What are the current good manufacturing practice regulations for medical gases? There are no specific medical gas regulations, so the requirements in the general CGMP regulations, Title 21, *Code of Federal Regulations*, Parts 210 and 211 with certain stated exceptions, are applicable for medical gases. In the preamble of the revised CGMP regulations issued on September 29, 1978, the agency recognized that medical gases were different from the traditional dosage forms in many respects.

So the first Compressed Medical Gases Guideline was issued in June of 1981, to assist the industry in understanding how the CGMPs apply to the manufacture of medical gases, with a subsequent revision in 1983. In February of 1989, the guideline was revised to address the evolving home care area, or the delivery of liquid oxygen to patients at home. We are currently working with industry to develop Fresh Air into the next official guidance document.

Let's briefly look at how FDA enforces the requirements and what our experience has been with the medical gases industry from a national standpoint.

FDA has the responsibility of enforcing the ***Federal Food, Drug, and Cosmetic Act (the Act)***. This law gives FDA the authority to conduct inspections, collect and analyze product samples to assure that foods, drugs, cosmetics, biologics, and medical devices are safe and meet the appropriate quality standards.

The Act states that a drug, such as medical oxygen, nitrous oxide, etc. is adulterated and subject to legal action if it is not manufactured in accordance with the CGMPs, or does not comply with appropriate official standards such as strength and quality as cited in the United States Pharmacopeia/National Formulary (U.S.P./NF).

According to the Act (section 501) a drug is deemed adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Section 510 of the Act requires all drug manufacturers, including fillers of medical gases, to REGISTER ANNUALLY with the agency and to list what products are produced, or filled. Failure to comply with this requirement is a violation of the law which can ultimately result in legal action.

Please note: One of the requirements for listing a firm's drug products is the submission of an actual specimen of the finished label(s) applied to the drug product(s). This would include high pressure cylinders, large cryogenic vessels and cryogenic home vessels. If a firm is utilizing a small, grocery-store type sticker to apply an expiration date, and/or a lot number to the product, the firm must submit a specimen along with its label on the Form FDA2657.

Once a firm is registered, FDA will automatically send the registration form back to the firm annually to verify the status of its operation. For registration and listing questions and to request the booklets and forms, contact the Product Information Management Branch @(301)594-1086.

Finally, section 704 of the Act authorizes FDA to enter each facility to conduct an INSPECTION to assess compliance with the law. Failure to permit an inspection is a violation of the law, which can eventuate in legal action. Under this section, FDA has the authority to collect and review all records, except financial data records that relate to the manufacture of a drug.

FDA is required by statute to inspect each registered drug facility at least once every two years. Often, inspections may occur more frequently, especially where FDA may suspect or know there is a problem with a specific firm or the industry as a whole.

If an inspection determines that a firm is significantly deviating from the CGMPs and satisfactory corrections have not been implemented, FDA will initiate regulatory action intended to prompt a firm to correct its problems and protect the patient.

There are several courses of action FDA can seek within the authority of the law, these include:

- issuance of a warning letter;
- seizure of a product, including storage tanks, high pressure cylinders, cryogenic home vessels on the premises, and trucks/vans containing the large cryogenic vessels, and tankers;
- an injunction;
- prosecution;
- disapproval of government contracts; and

- informing the Health Care Finance Administration.

Let's look at the general state of compliance in the compressed medical gases industry today? We are finding that the general state of CGMP compliance is not very good. This is evident by the data contained in the following slides which represents the total number of warning letters and seizures for the fiscal years of 1994 to 1999. For warning letter: in '94' - 91; in '95'- 109, in '96' - 103, in '97' - 152, in '98' - 76, and in '99' - 79. The next slide shows the seizure actions approved, 15 in '94', 11 in '95', 6 in '96', 7 in '97', 8 in '98', and 12 in '99'. We have had one injunction and two prosecutions. In FY99, we have had one civil contempt and one inspectional warrant.

This regulatory action rate indicates a need for the industry to improve its overall compliance with the CGMPs.

NOTE: In accordance with the Regulatory Procedures Manual - August 1997, Chapter 10, FDA is under no legal obligation to warn firms or individuals that they or their products are in violation of the law prior to taking formal regulatory action. If a firm has multiple locations, and if any one of these locations receives a warning letter for significant CGMP violations, a meeting, an FDA483, etc., and the responsible persons have been advised, and if another inspection finds continuing violations of the nature reported in the prior warning, then FDA has the option to proceed immediately to a seizure or an injunction.

Next, let's look at the CGMPs that a manufacturer of medical gases is expected to follow. A word of **CAUTION**, please check the accuracy of any information you may receive with FDA before changing or implementing a possible violative CGMP practice or procedure.

RESPONSIBILITY OF QUALITY CONTROL UNIT

Section 211.22(a)

Each firm is required to establish a quality control unit (QCU) having the responsibility and authority to approve or reject all drug product containers, closures, in-process materials, labeling, written procedures, the authority to review production records to assure completeness and accuracy, and is responsible for the approval or rejection of all manufactured drug product.

The responsibilities and procedures applicable to the QCU must be in writing and must be followed. The designated person(s) are required to meet the Personnel Qualifications requirements listed below [211.25], must be identified in the firm's procedures, and must

receive appropriate quality assurance training. A small firm may designate a single individual with the above responsibilities.

For air separation plants (ASU), prior to release of the drug product, especially at night, a designated QCU employee must be the final signature for release of the drug product. A firm must not allow a third party consignee, i.e., firm receiving the load to sign off as the ASU's QCU.

PERSONNEL QUALIFICATIONS

Section 211.25(a)

In any manufacturing operation involving human manipulation there are hazards which may be created by preoccupation, mental lapse, carelessness and the like. Therefore, all on-the-job and CGMP training should be revisited at frequent intervals and needs to be conducted by qualified individuals.

A firm is expected to establish detailed written procedures (training program) outlining the specific areas of the firm's operation to be covered. On-the-job training is acceptable, as long as the training is conducted by a qualified individual on a frequent basis. Any employee involved in the manufacturing, filling, processing, handling, holding, or shipping of a medical drug is required to be trained both on-the-job and in the CGMPs. This would include all delivery and/or truck drivers who deliver medical drug products.

The lack of CGMP training is one of the most overlooked areas observed at most medical gas firms. CGMP training should be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with the CGMP requirements that are applicable to their function. Conducting CGMP training once a year is not recommended, but instead should be presented in smaller more manageable portions, presented throughout the year with documentation of the type, time, and attendance of each session.

All training must be documented.

Additional information may be obtained from:

1) FDA websites where an individual may review and retrieve: 1) the quarterly publication, The Human Drug CGMP Notes that addresses policy questions and other pressing issues under the GAS WHAT? column, 2) the current edition of the Fresh Air presentation, and 3) the CGMPs. To obtain an electronic version of these documents, using the Internet type: <http://www.fda.gov/cder/dmpq/cgmpnotes.htm>, or [gases.htm](http://www.fda.gov/cder/dmpq/gases.htm), or [cgmpregs.htm](http://www.fda.gov/cder/dmpq/cgmpregs.htm), respectively.

For those individuals or firms that do not have access to the Internet, please check with your local public library who usually allow free use of their computers and access to the Internet.

Under the Medical Gas Home Page [<http://www.fda.gov/cder/dmpq/gases.htm>], Medical Gas Regulatory Actions is a listing of all warning letters issued for Fiscal Year 1993 to the present.

2) the Superintendent of Documents at (202)783-3238 for a copy of Title 21, Code of Federal Regulations, Parts 200 - 299.

3) the firm's supplier who may be offering CGMP training and other types of training for their consignees throughout the year.

4) a qualified medical gas consultant or consulting firm, and

5) the Compressed Gas Association at (703)412-0900 for their educational pamphlets, bulletins, and videos, or the National Welding Supply Association at (215)564-3484.

CONSULTANTS

Section 211.34

All consultants advising on the manufacture, processing, packing, or holding of a medical gas must have sufficient education, training, and experience, or a combination thereof, to advise on the related subject for which they are hired.

A firm must maintain records stating the name, address, and 'qualifications' of any consultants and the type service they are to provide.

DESIGN AND CONSTRUCTION

Section 211.42

Any building, van, truck, etc. used in the manufacture, processing, holding, or delivery of a medical gas should be of suitable size and design. There should be adequate space for the orderly placement of equipment and materials to prevent mix-ups and or contamination.

Quarantine areas should be set up to separate the incoming drug product, incoming cylinders and vessels, equipment, rejected containers, and the finished product prior to release.

Delivery trucks should have a well defined and separate area for medical drug products and one for industrial grade products.

EQUIPMENT CLEANING AND MAINTENANCE

Sections 211.67(a)

All equipment used in the manufacturing of a drug product shall be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug.

The Commissioner intended that containers and closures be clean before use. In some instances this will require the manufacturer to perform separate, and sometimes extensive, cleaning cycles, while in other instances it would not be necessary. A word of caution, equipment used to supply industrial grade product is required to be cleaned, and qualified before introducing a medical gas.

If the possibility exists that a medical product, equipment, or containers or closures may have been exposed to a contaminant(s), then a test for that contaminant(s) is required. The U.S.P. General Notices, Foreign Substances and Impurities section states it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present. Therefore, the U.S.P. monograph is not a total impurities screen. In fact, your testing procedures should address all possible contaminants your equipment may encounter, including high pressure cylinders and cryogenic vessels.

EQUIPMENT CALIBRATION

Section 211.68

A firm should establish written procedures addressing a calibration schedule for all equipment used during its operations. A firm may reference in the written procedures the manufacturer's instruction manual for the recommended calibration schedule, as long as the manual is available and is followed to assure proper functioning of all equipment. This would include pressure gauges, vacuum gauges, thermometers, scales, etc.

A firm can either use the manufacturer's recommended calibration frequency or can use historical data developed by the firm, but a firm cannot merely assume a frequency time unless supported by data.

Vacuum gauges are required to undergo two (2) calibrations. The first calibration which is performed on a daily basis with no vacuum present, is a check to assure that the needle on the gauge returns to 'zero.' This daily check should be recorded on the batch production record or a separate log. The second and more significant calibration requires the vacuum gauge to be calibrated to standards established by the National Institute of Standards and Technology. The frequency of calibration should be the manufacturer's requirements, or a firm could establish their own calibration schedule from their historical data.

Likewise, thermometers are required to be calibrated in accordance with the manufacturer's recommendations, or a firm may establish their own calibration schedule from their historical data. This calibration is required to be documented in a separate log.

Recently, we have encountered problems in the industry with the use of check valves in a firm's supply system to prevent the back flow of foreign or contamination into the lines. It has been our experience that these check valves can be compromised such that a proper seal fails to occur. Therefore, prior to using any check valve, a firm must perform a validation study to assure they are acceptable for use. A recent recall involved the contamination of high pressure cylinders with oxygen compatible oil which contaminated the system following a vacuum pump explosion which forced the oil past the 'check valve.'

Check valves are often placed at various points in supply lines to protect the pump, manifold or other equipment from over pressurization or an undesirable back flow. Check valves that are only intended to act as an added safety feature and are not used to prevent the cross contamination of gases or impact product identity, strength, purity, or quality are not required to be validated. Please refer to the September 1994, edition of the Human Drug CGMP Notes.

Low pressure gauges used for the filling of cryogenic home vessels do not require N.I.S.T. traceability, nor require calibration. Likewise, flow meters are not required to be calibrated.

COMPUTER SYSTEMS VALIDATION

All computer systems are required to be validated. Before a firm converts any of its manual operations to an automated operation that will be controlled by a computer system and associated software, it is required to validate the computer system and associated software.

According to the Guideline on General Principles of Process Validation, May 1987, validation is defined as establishing documented evidence which provides a high degree of assurance a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Computer Validation references:

Micron Video International, Inc. - Videocassette 'The GMP of Validation Understanding Validation' (Module No. GMP/M-083), telephone number 1-800-5-Micron or 336-294-7116. Some of the areas addressed are: What is validation? Why & when to validate; Definitions; The principles of validation; Positive benefits; Validation Methods; Validation plans and protocols; Qualification explained; Validation of computer controlled systems; and 3 case studies.

Good Computer Validation Practices - Common Sense Implementation by Teri Stokes, Ronald C. Branning, Kenneth G. Chapman, Heinrich Hambloch, and Anthony J. Trill, Interpharm Press, Inc. (303)754-3953 or (303)662-9101.

PDA Journal of Pharmaceutical Science and Technology, Technical Report #18, 1995, Volume 49, Number S1, Validation of Computer-Related Systems.

Pharmaceutical Engineering, July/August 1995, Computer Systems Validation: A Historical Perspective by Dr. Guy Wingate.

Pharmaceutical Technology, March, April & May 1992, GMP Documentation Requirements for Automated Systems: Part I, II, & III, respectively.

The addition of portable or add-on racks, etc. via pigtails to the main header or manifold requires a validation to assure the cylinders on the portable rack are being properly vacuum evacuated, and are being filled to the correct service pressure.

COMPONENTS

Section 211.80 to 94

Drug product containers and closures play a critical role in assuring that the drug product provided to the patient is has the appropriate same strength, quality, and purity. This presents unique risks to be considered that are not present in other industries where the containers and closures are used only once. Therefore, all high pressure cylinders and all cryogenic vessels and their associated valves are required to undergo strict prefill inspections, prior to filling with a medical gas.

We have received several reports of patients suffering injuries due to high pressure cylinders that were contaminated with unusual chemicals, such as freon 14, benzene, chlorine, etc. All high pressure cylinders are required to be cleaned, prior to the introduction of a medical gas. Adequate cleaning procedures should be established and followed in order to prevent any contamination or impurities from being introduced into a medical drug container. The agency is currently investigating the possibility of requiring dedicated medical drug containers.

Prefill Inspections

1. High Pressure Cylinders

Under the CGMPs, a firm is required to perform the following procedures on each and every cylinder, except as specified:

- **hydrostatic testing date [cylinder markings]** - Steel cylinders are tested every five (5) years, unless a "*" follows the testing date which means the cylinder may be tested every ten (10) years. Aluminum cylinders must undergo testing every five (5) years.

The use of one hundred percent ultrasonic inspection of steel high pressure cylinders in lieu of the internal visual and hydrostatic retest, is acceptable. This practice is becoming more wide spread.

Certain cylinders, such as fiber wrapped cylinders, etc. are manufactured under an exemption and have unique requirements pertaining to test date intervals and length of service life.

- an **external examination** of each cylinder looking for dents, arc burns, dings, oil, grease, and other signs of external damage, including fire or thermal damage that might cause a cylinder to be unacceptable or unsafe for use.
- **venting or blowing down** the cylinder to atmospheric pressure if any gas is present; or inverted and drained if it contains a liquid product.
- an **odor or sniff test** to detect the presence of any foreign gas or other odor. (This test must not be performed on carbon dioxide, nitrous oxide, or anesthetic gases.)

If a cylinder is received empty, i.e., no pressure, in order to perform the odor test a medical grade product [FDA recommends the use of an inert gas similar to Nitrogen NF] should be introduced into the cylinder at a predetermined pressure. An odor test is performed on the resulting gas. Under no circumstances can a firm use industrial grade product due to the possible presence of industrial contaminants. This practice must be described in detail in a firm's written procedures.

- a **hammer or dead ring test** which is a valuable indicator of internal corrosion. This procedure must be performed on empty unpressurized cylinders with a 10 year retest date. [Cylinders with a 5 year test date are not required to undergo a hammer test.] The hammer test consists of tapping the cylinder sidewall with a light blow using a ball-peen hammer, etc. A good cylinder will make a clear bell-like ring, while a dull ring indicates possible internal corrosion. All cylinders with a dull ring should be marked as unacceptable and quarantined.

This procedure must not be performed on aluminum or certain other cylinders as their materials of construction do not lend themselves to the same ability to provide an indication of internal corrosion.

- the **valve assembly** must be examined for the presence of debris, oil or grease which should be removed before use, and for the correct CGA valve which is unique for the specific medical gas. Recent problems encountered with valve assemblies has necessitated stricter inspections:
 - are any of the threads on the valve or on the top of the valve stem damaged?
 - is the handwheel or valve stem bent?
 - are there noticeable signs of damage?
 - are there visible signs of corrosion inside the valve?
 - are there visible signs of excessive heat or fire damage?
- **the correct color** for the corresponding medical gas. The medical gas industry uses a color code system to aid in the identification of a medical gas cylinder. A firm should not rely solely on the color coding for identification of the medical gas to be filled. Instead, a firm should rely on the drug product label.

- the **label**. Old labels need not be removed if they are identical to the labels currently acceptable, are in good condition and are applicable to the product being filled. However, obsolete labels or labels containing old lot numbers should be removed. A firm may not apply one label on top of another label.
- **vacuum evacuation**. Residual gas must be removed from each cylinder by means of a vacuum pump capable of pulling a vacuum of at least 25 inches of mercury at sea level before oxygen or any other medical gas is introduced into the filling manifold.

Cylinders failing any of these prefill procedures are required to be quarantined to a separate area to prevent their use in the subsequent filling process.

All of the above high pressure prefill inspections are required to be documented on a batch production record under specific and appropriate headings.

2. Cryogenic home vessels (patient specific containers)

Cryogenic home vessels are required to undergo certain prefill inspections, prior to filling. The required prefill inspections are usually contained in the manufacturer's manual supplied with each cryogenic vessel. At a minimum there should be:

- an external vessel inspection,
- ***all inlet and outlet connection inspection***,
- a volume or contents gauge inspection, and
- a label inspection. The firm filling a cryogenic home vessel must apply a drug label.

Documentation that each cryogenic home vessel has undergone the above inspections must be entered on a cryogenic home vessel batch production record under specific and appropriate headings. A possession sticker is not an acceptable label.

3. Large cryogenic vessels

Large cryogenic vessels should be dedicated to medical use only, and are required to undergo specific prefill inspections, prior to filling. At a minimum there should be:

- an external vessel inspection,
- ***all inlet and outlet connection inspection***
- ***permanently brazened fitting or connection in place, i.e., both the inlet and outlet; or utilize a tamper-evident device on each fitting or connection,***
- an inspection for the DOT markings,
- an inspection to ensure the pressure relief device on the unit is appropriate for its intended use, and
- a label inspection. Any firm filling a cryogenic vessel must apply a drug label.
- ***on the dome a medical product designation, i.e., Oxygen U.S.P. under each fitting or connection, or a 360 degree wrap-around tape at the top of the vessel.***

FILLING OPERATION

The two most common methods of filling high pressure cylinders are:

a) Liquid to Gas. During this practice, liquid oxygen is pumped from a storage tank through a vaporizer or heat exchanger converting the liquid into a gas which travels through piping to a filling control system. Attached to the filling control system will be a filling manifold usually with multiple outlets to which the high pressure cylinders are attached to be filled; or

b) Gas to Gas, commonly referred to as cascading [See Definition #1].

During the filling operation, the filler is required to perform a heat of compression check which is accomplished by lightly touching the exterior of each and every cylinder undergoing filling. A warm cylinder indicates the cylinder is filling properly, while a cool or cold cylinder may not be filling properly, and should be investigated and addressed.

CHARGE-IN COMPONENTS

Section 211.101a

Each batch shall be formulated with the intent to provide at least 100 percent of the labeled

medical gas; therefore, each cylinder should be filled to the indicated net content statement listed on the label.

Temperature & Pressure [Boyle's Law]

A gas in a closed container, such as a high pressure cylinder, will increase in pressure as the temperature of the gas rises. Overfilled cylinders could reach dangerously high pressures if exposed to elevated temperatures, even if their pressure at room temperature is safe. This temperature rise must be properly compensated for during filling to assure that the authorized pressure is not exceeded and the content meets or exceeds the net content statement listed on the label.

Since temperature and pressure are directly proportional a temperature pressure chart or other temperature-pressure calculation algorithms that are used to adjust the filling pressure so that the proper contents are achieved (generally stated as the pressure at 70 degrees F with appropriate tolerances). Filling temperatures measured on the wall of a cylinder cannot exceed 130 degrees F for safety reasons. If a firm is filling one cylinder at a time via the cascade method, then a thermometer must be attached to each cylinder filled.

Prior to shutting off the gas flow via the valves, the temperature and pressure reading must be recorded on the batch production record.

NOTE: FDA's temperature and pressure requirement should not be confused with the Department of Transportation's, Title 49 CFR 173.302(e): Verification of container pressure. Each day, the pressure in a high pressure cylinder representative of that day's compression must be checked by the charging plant after the container has cooled to a settled temperature and a record of this test kept for at least 30 days.

If a "+" symbol follows the hydrostatic testing date, then a cylinder qualifies for a ten percent (10%) overfill unless the valve is equipped with a fusible, metal-backed safety. These are usually found on post valves for gaseous fills only. Aluminum cylinders must never be overfilled.

Valve Assembly Leak Testing

During the filling operation, the first of the two required valve assembly leak tests must be performed. At this time, each cylinder valve assembly is tested for valve packing leaks, safety plug leaks and other valve leaks using a leak detecting solution. The valve packing leak test is required to be performed with the cylinder under pressure and while the cylinder valve is opened.

Routinely, a leak detection solution is sprayed on and around the entire valve assembly, looking for bubbles indicating a leak. This solution must be oxygen compatible and must not contain any hydrocarbons. Solutions containing soap are not recommended since they may be corrosive to the valve stem and may develop a residue buildup.

RETESTING OF CONTAINERS

Section 211.87

Containers and closures for medical gases are required to be retested for identity, strength, quality, and purity and approved or rejected by the quality control unit, after exposure to conditions that might adversely affect the drug product container or closure. This would pertain to any container or closure used to deliver industrial products, any new cryogenic home vessels or any portable unit.

If a cryogenic home vessel is new, repaired or if maintenance is required, then upon return and after filling, the vessel should be retested for identification, prior to redistribution.

WRITTEN PROCEDURES

Section 211.100(a & b)

There cannot be different standards of quality of drug products for large and small manufacturers. Written procedures regardless of the size or complexity of the operation must be established. They provide a basis for the uniform performance of a function, and they provide a step-by-step description on how to perform a specific task, function, or operation.

All firms are expected to establish and follow detailed written procedures covering all aspects of their operation to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, are to be reviewed, signed, dated, and approved by the firm's quality control unit.

In addition, it does little good to enact new procedures and controls if they are not read, understood, and followed by all employees, and readily available.

This presentation cannot and must not be used as a firm's written operating procedures.

CALCULATION OF YIELD

Section 211.103 & 184(c)

At the current time, we are not enforcing the calculation of actual yields and percentages of the theoretical yield as required by Section 211.103 and from the 211.184(c) requirement that records should include an individual inventory record of each component, and a reconciliation of the use of each lot of component.

PACKAGING AND LABELING CONTROL

Sections 211.122, 125, & 130

A firm must establish written labeling procedures covering the receipt, identification, storage, handling and examination of all labeling. Procedures should cover the reconciliation, issuance, returns, and security of labeling. There must be written procedures to assure that the correct label is used on the drug product, including the identification of each batch with a lot number.

All high pressure cylinders, large cryogenic vessels and cryogenic home vessels are required to bear an adequate drug product label. This label is usually the responsibility of the manufacturer, filler, transfiller, etc.

NOTE: There can be only one drug label on a high pressure cylinder or cryogenic vessel, and that label is usually applied by the manufacturer, filler, transfiller, etc. of the drug product. Cryogenic home vessels come from the manufacturer with a DEVICE label, which should not be confused with the required drug label. Further, the device label must not be removed. Cylinders owned by one company, but filled by another company may bear a small ownership or possession sticker in addition to the drug product label.

Upon receipt from the printer, a new batch of labels must be counted to verify the quantity of labels received, and they should be examined and compared against the approved master label to assure correctness.

If a firm uses a small, grocery-store type sticker to contain an expiration date or a lot number, then this practice should be addressed in a firm's written procedures. Further, these stickers must not fall off, or the drug product is misbranded.

Section 503 of the Act requires prescription drugs to bear the statement: "Rx Only."

However, if a firm sells Oxygen U.S.P. to emergency medical services, i.e., fire departments, rescue squads, ambulance companies, etc. or for emergency use, then the label is required to contain the statement: **"For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Rx Only."**

A firm may continue to use the old statement, "Caution: Federal law prohibits dispensing without prescription" on its label and still be in compliance. However, at the next printing of labels or no later than February 19, 2003, the new "Rx Only" statement must be used.

LOT NUMBERS

According to the CGMPs, each manifold filling sequence, each uninterrupted filling sequence, each cryogenic vessel filled, and each storage tank following a delivery is considered a new lot and is required to be assigned a new lot number.

The assigning of a single lot number for an entire days production is not acceptable. A manufacturing operation, such as the filling of high pressure cylinders on a multi-outlet manifold, is governed by a set of manufacturing procedures or conditions which when performed from the beginning to the end of a process provides assurance that the batch is uniform and consistent. As such, each batch is in itself a separate entity with its filling operations unique to that filling sequence.

For firms filling liquid oxygen for delivery to home patients, each of the large cryogenic vessels or dewars either portable or permanently mounted in a van or a truck are required to be assigned a unique lot number.

At the present time, cryogenic home vessels filled at a patient's home, i.e., curbside, are not required to bear a lot number. However, cryogenic home vessels filled on site and stored for future delivery, or cryogenic home vessels filled by a third party, require lot numbers.

Labels should be carefully removed to prevent damage to the cylinder.

EXPIRATION DATING AND STABILITY TESTING

Sections 211.137 & 166

The Compressed Gas Association submitted a citizens petition to exempt medical gases from compliance with the expiration dating requirements of 21 CFR 211.137. While FDA evaluates the data, we are not enforcing this requirement. However, if a firm's written procedures call for an expiration date, then we would expect a firm to be following their procedures and apply an expiration date to the product.

Medical gases or medical gas mixtures that are considered new drugs or investigational new drugs are required to undergo stability testing in order to establish an appropriate expiration date.

HOLDING & DISTRIBUTION

Sections 211.142 & 150

Section 211.142 states written procedures should be established describing the warehousing of the drug product including the quarantining of the finished drug product, prior to release.

Section 211.150 states there should be written procedures describing a system by which the distribution of each lot of drug product can be readily determined to facilitate a recall if necessary.

Please note that reliance on a system of contacting every customer in case of recall is not sound. Under this type of system recalls could be delayed if customers who received recalled products were not contacted because they were not customers at the time of initiation of the recall. Conversely, customers who never received the product could be contacted, thus taxing the resources of the firm and FDA. A blanket recall might also cause unneeded patient anxiety, and the Commissioner does not believe that the same accountability for each lot is inherent in a system that relies on contacting every customer.

These procedures should include appropriate descriptions of the firm's methods of segregation while the medical gas products are in storage/warehousing and on delivery vehicles. Specifically, firms should establish adequate areas so employees are able to delineate between: 1) industrial grade vs. medical grade, for the same gas; 2) empty vs. full vs. in-process containers; and 3) containers of different medical gases.

LABORATORY CONTROLS

Sections 211.160(a) & 160(b)(4)

Section 211.160(a) - Written procedures covering any specifications, standards, sampling plans, and testing should be established and followed to assure that each batch of drug product conforms to final specifications.

A firm should describe how many cylinders or cryogenic vessels are to be tested, when that testing is to occur, the acceptance criteria, and the course of action to be taken if test results fall outside of established specifications. This is especially significant for firms filling high pressure cylinders one at a time.

Section 211.160(b)(4) - Oxygen analyzers, instruments, gauges, etc. must be calibrated at suitable intervals in accordance with the manufacturer's instructions.

CALIBRATION STANDARDS

All testing equipment used to analyze a drug product is required to be calibrated with certified calibration standards to ensure proper operation. Gas calibration standards must be manufactured by methods which ensure the proper level of precision and accuracy reported on the COA, and are appropriate for the method in which the standard will be used. Due to the level of scientific sophistication needed to properly produce a calibration standard, calibration gases should be manufactured only by firms using appropriate equipment, qualified personnel, and standard gases.

Gas calibration standards must be appropriately labeled, cannot be medical grade or industrial grade, and must be accompanied by a certificate of analysis certifying the actual test results.

COA - Calibration Standards

Each COA for a gas calibration standard is specific for that particular cylinder, and should provide the following information:

- 1) Supplier's name and complete address
 - 2) Name of the Product (Cannot be medical or industrial grade)
 - 3) Lot Number or unique identification number
 - 4) The analytical methodology used to assay the standard
 - 5) The Actual Analytical results obtained, i.e., 99.9% Nitrogen. All other components are identified on this document.
- 4) Supplier's signature and the date.

After the filling operation is completed, the **second valve assembly leak test** is performed. This test detects any valve outlet leaks. If any leaks are detected, the cylinder should be removed from service and quarantined until repairs can be made.

TESTING AND RELEASE

Sections 211.165(a) & 165(e)

Due to the uniqueness of filling medical gases, each firm is required to determine the identity and strength of 1) the incoming drug product, and 2) the drug product delivered to a consignee, customer, or patient. Testing should be by appropriate methods to determine conformance with official specifications, either using 1) the U.S.P. testing methodology, or 2) a validated test procedure capable of producing equivalent or greater than U.S.P. test results.

If a failing test result is obtained, resampling or retesting is not allowed, unless and until a thorough investigation performed in accordance with established written procedures. For further guidance, please refer to the draft Guidance for Industry Investigating Out-Of-Specification (OOS) Test Results for Pharmaceutical Production which is available on FDA's website.

The testing requirements for high pressure cylinders 1) filled on a multiple outlet manifold is one cylinder from each manifold filling sequence must be assayed for identity, strength, and odor, or 2) filled individually, one cylinder per uninterrupted filling sequence must be tested for identity, strength, and odor. See Glossary definition # 14 for details.

According to the U.S.P. a finished product odor test is required to be performed on each high pressure cylinder tested. This odor test should not be confused with the required prefill odor test, and is required to be recorded on either the batch production record or a separate testing log. An odor test should not be performed directly on any liquid due to the possibility of frostbite. However, an odor test may be performed on a vaporized sample of the liquid product obtained through the product withdrawal connection on the liquid vessel.

A firm cannot receive industrial grade product and simply perform the U.S.P. tests to convert it into a medical grade product. This practice is commonly known as testing CGMP into the product. Testing alone will not provide assurance that the product was manufactured under CGMP, which must be present throughout the entire manufacturing process. Therefore, a firm must receive medical grade product in order to supply medical grade product. Medical grade product may be used for other applications, such as foods, beverages, even industrial uses, but cannot bear the U.S.P./NF designation on the label.

LIQUID TO LIQUID FILLING - Oxygen ONLY

This section pertains to firms that fill medical grade oxygen only, into cryogenic home vessels, either at a patient's home, i.e., curbside or at a firm's location, i.e., onsite. Should the firm fill any other type of liquid, then this section is not applicable.

1. TESTING OF THE INCOMING LIQUID OXYGEN

If a firm dispenses liquid oxygen (LOX) from large cryogenic vessels into cryogenic home vessels, then one of the following procedures must be complied with:

Please note all of the conditions listed under each of the following testing scenarios must be met in order to satisfy that requirement.

- a) No testing would be required, as long as the receiving firm witnesses the testing, i.e., identity and strength of each large cryogenic vessel by the supplier, receives a valid COA for each vessel, and documents that the testing has been witnessed.

In addition: The employee responsible for witnessing the testing is required to receive training specific to the analytical methodology being witnessed, and this training should be documented and maintained on file by the employee's firm.

- b) If the testing is not witnessed, then the receiving firm may rely on a valid COA for the strength determination, but must perform an identity test on **EACH** large cryogenic vessel received or filled by the supplier. The firm is required to periodically verify the reliability of the supplier's analysis which should be performed at least once a year by:

- 1) visiting the supplier to:

- determine if the supplier is registered with FDA;
- assure the supplier is following appropriate written testing procedures;
- witness analytical testing being performed, including calibration of the analyzer;
and
- document that the above was performed, or

- 2) taking a sample from a recent delivery to a third party for analysis for conformance with U.S.P. specifications.

- c) If a firm fails to comply with either method (a) or (b), then full U.S.P. testing would be required on the incoming drug product, i.e., each large cryogenic vessel.

2. TESTING OF A STORAGE TANK

Under this scenario, a storage tank is located on the firm's premises and used to fill either vehicle mounted vessels which in turn are used to fill cryogenic home vessels at a patient's home or cryogenic home vessels on site. Again, this section is specific to firms who fill liquid oxygen only.

Combining a new shipment of drug into a storage tank, or any cryogenic vessel with the remainder of a previously received, tested, and approved lot causes the commingling of the material. The result is that the previously approved material becomes an integral part of an unapproved new lot and cannot be used until such lot is approved for use.

An identity and strength test must be taken directly from the storage tank after each oxygen delivery, prior to the filling of any cryogenic vessels, including cryogenic home vessels. Large cryogenic vessels filled from this storage tank need not be tested as long as:

- a) No other storage tank(s) is located on the premises;
- b) They are dedicated to the delivery of oxygen by the firm for home care use only;
- c) They have not been completely emptied or have not been out of service. [If the vessel is _liquid empty. i.e., without liquid oxygen_ AND has a gaseous pressure below 15 psig, the vessel should be requalified for full U.S.P. testing]; and
- d) A valid certificate of analysis is received with each delivery, and maintained on file.

3. TESTING OF CRYOGENIC HOME VESSELS

The most significant condition in the filling of liquid oxygen into a cryogenic home vessels is the control of the home vessels. If the possibility exists that a contaminant or a foreign product could be introduced into the cryogenic home vessel, then additional testing may be required. Each firm must be aware of situations in their business that might cause such contamination, and to develop appropriate methods to control them.

One of the following procedures should be followed:

- a) No testing of the cryogenic home vessels would be required as long as all of the following criteria are met:

- 1) liquid oxygen is the only liquid being filled on the premises;
 - 2) the incoming liquid oxygen is adequately tested according to one of the methods outlined under Items #1 (Testing of Incoming Liquid Oxygen) and 2 (Testing of a Storage Tank); and
 - 3) the cryogenic home vessels are filled by the firm
- b) If any other liquid is being filled on site or if the incoming liquid oxygen is not tested in accordance with one of the methods outlined under Items #1 and 2, then ALL cryogenic home vessels filled are required to be tested for full U.S.P. specifications.
- c) If a home care company (HCC) has their cryogenic home vessels filled by another individual or firm, then prior to delivery, the HCC is required to inspect each vessel to assure a correct label including a lot number has been applied by the filling firm, prior to release to the patient. The filler of the CHVs is responsible for ensuring the vessels are properly filled, tested, and labeled including a lot number.

Additional CGMP requirements for this operation are the HCC must establish written procedures addressing distribution, recall, and complaints and complaint files.

This concludes the testing requirements for the filling of medical oxygen only.

LIQUID TO GAS and FILLING LARGE CRYOGENIC VESSELS

This section pertains to firms such as welding supply companies that fill many types and forms of medical gases, where the potential for mix-ups is greater.

This operation involves the filling of high pressure cylinders via a heat exchanger or a vaporizer, and the filling of large cryogenic vessels. The testing requirement is immediately after each delivery, the commingled liquid oxygen must be tested for full U.S.P. specifications. This may be accomplished by:

- 1) taking a sample directly from the storage tank, or
- 2) testing a cylinder from the first filling sequence (manifold or rack) which is the most commonly seen practice.

A storage tank is required to be tested prior to the filling of a medical product.

Each and every cryogenic vessel filled is required to be tested prior to release, since cryogenic vessels usually contain residual product and a commingling of new and old product results. This commingling produces a new batch or lot and is required to be analyzed and assigned a new batch or lot number. A valid certificate of analysis should be provided with each cryogenic vessel, and the COA should be maintained on file.

What is the official method outlined in the current edition of the United States Pharmacopeia (U.S.P.).

Oxygen Monograph

The U.S.P. oxygen monograph lists the potency as being not less than 99.0% by volume of O₂. It also states that oxygen produced by **the air liquefaction process** is exempt from the requirements of the test for Carbon dioxide and Carbon monoxide.

Note: If a firm fills Oxygen U.S.P. and fails to have a certificate on file documenting that the oxygen is produced by the air liquefaction process, or if the label lacks this statement, then a firm is required to perform the contaminant tests for carbon dioxide and carbon monoxide test, not just an identity, strength, and odor test.

The official method which is commonly referred to as the "ORSAT" buret method utilizes a calibrated 100 ml buret, copper wire, and ammonium chloride and ammonium hydroxide solutions which are mixed together and equilibrated by agitation with the copper wire. A 100.0 ml sample of the unknown gas is drawn into the buret and agitated, the residual gas is then measured.

In addition, a specific identity test is required to be performed at the same time, since carbon dioxide is capable of giving similar results. This is usually accomplished by using either a carbon dioxide detector tube.

Finally, a finished drug product odor test must be performed on each container undergoing testing.

The accuracy of the U.S.P. procedure is +0.1%.

The General Notices, Foreign Substances and Impurities states while one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination.

These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

LIQUIDIFIED COMPRESSED GAS

Because the pressure in a closed vessel containing carbon dioxide and nitrous oxide will increase with a rise in temperature, the possibility always exists that a cylinder filled at a safe pressure at normal temperatures might reach a dangerously high pressure at high ambient temperatures. Therefore, nitrous oxide and carbon dioxide are filled individually on a scale, as liquids where pressure does not indicate the amount filled. These cylinders are filled individually by weight which should not exceed 68% of the weight of water the cylinder will hold at 60oF (15.6oC).

One cylinder filled during an uninterrupted filling sequence should be tested for identity and strength, prior to release.

Because carbon dioxide and nitrous oxide can mix, and not be differentiated or detected by the U.S.P. or the pressure differential method, a carbon dioxide test must be performed concurrently with the assay to assure identity of nitrous oxide or carbon dioxide. The pressure differential method has been evaluated and found to be an acceptable alternative testing methodology. ***However, a firm must maintain on file the actual validation study in accordance with 211.165(e).***

If a carbon dioxide identity test is not performed concurrently, then the analysis for the finished drug product is not acceptable.

GAS MIXTURES

If the product is a mixture of two gases, then every cylinder should be tested for the identity and strength of one of the gases, usually the active ingredient. In addition, an identity test for the other gas should be performed on one cylinder from the manifold filling sequence.

For a mixture containing three gases, every cylinder should be tested for the identity and strength of two of the gases, and one cylinder from each manifold filling sequence should be tested for the identity of the third gas.

Testing of Nitrogen NF

At the current time, all firms receiving shipments of Nitrogen NF, must meet all of the following criteria. Once a firm has complied with the following, then the firm would not be required to utilize a gas chromatograph to assay the finished drug product which is the official U.S.P. testing methodology.

- 1) the supplier of the incoming nitrogen must be registered with FDA;
- 2) a valid certificate of analysis is received with each delivery and the product must be designated as Nitrogen NF;
- 3) the filling system has dedicated lines, and these supply lines are traceable from the storage tank to the filling manifold. If there exists a possibility that another gas, whether it be industrial or medical, could be introduced and contaminate the product, then in addition to full U.S.P. testing, a test for the absence of the contaminating gas is required;
- 4) testing for the lack of oxygen, i.e., less than or equal to 1.0%. This may be accomplished with an oxygen analyzer having the capability of producing results between 0 - 1%, and being properly validated against the U.S.P. methodology [See section 211.165(e) below].

In addition, the oxygen analyzer must be properly calibrated for the potency of the tested product, i.e., less than or equal to 1.0%; and

- 5) perform a supplier audit, **annually. If a firm is unable to perform an annual audit, then the CGMPs require full U.S.P. testing.**

Note: Nitrogen used to cool devices, such as probes used to contact body parts, or used for any other "physical effects" or "function through physical action to the body to cool or freeze tissues for therapeutic action" is a device. Any firm providing this type of product would be required to register and list with the Center for Devices and Radiological Health and to comply with the device CGMPs.

Alternative Testing Methods

Sections 211.165(e)

If an alternate testing method, i.e., a non-U.S.P./NF methodology is to be used for the analysis

of medical gases, then the accuracy, sensitivity, and reproducibility of the method is required to be established and documented. This would include changes to the analytical methodology, such as a different column length, or a different carrier gas, etc.

Each firm is required to maintain on file a copy of the actual validation protocol including the data generated for each analyzer by model number, demonstrating U.S.P. equivalency. Further, the manufacturer's instruction manual must be on file to assure proper calibration of the analytical equipment. This would include all Servomex oxygen analyzers.

The current edition of the U.S.P. 24 <1225>, page 2149, titled Validation of Compendial Methods must be used to perform any equivalent testing. Please note this edition contains additional criteria that must be met.

On the other hand, properly calibrated [using calibration standards] handheld oxygen analyzers provide a specific oxygen identification test result only, and thus are not suitable for performing U.S.P. assay testing. At the present time, we are unaware of any of these instruments having the accuracy required to provide an equivalent Oxygen U.S.P. strength result. Typically, these analyzers have an accuracy of + 1 to 3%, not the required +0.1%.

RECORDS & REPORTS

Section 211.180(a) & 182

Any record required by the CGMPs must be maintained in compliance with this part. This would include training records, certificates of analysis, equipment cleaning & calibration logs, label reconciliation logs, master production records, batch production records, analytical equipment calibration logs, testing records, complaints files, etc.

During an inspection, if the record review by FDA's investigator reveals no record, incomplete records, or significant steps have not been documented, then FDA assumes the operation, practice, step, etc. was not accomplished.

Record retention requirements: 1) if an expiration date is used, then all records must be retained for at least one (1) year after the expiration date of the batch, or 2) if no expiration date is used, then records must be retained for at least 3 years after distribution of the batch. [This requirement may change once FDA has completed its review of the CGA's citizen petition requesting exemption from expiration dating.]

Records may be in the form of true copies or electronic copies.

The Electronic Records and Electronic Signatures regulations [21 CFR Part 11] became effective on August 20, 1997; therefore, prior to converting a firm's operation from paper to electronic records, a firm must comply with these regulation.

MASTER PRODUCTION AND CONTROL RECORDS

Section 211.186

While master production and control records are required, this requirement may be met by establishing a manual containing all written operating procedures, an actual specimen of each label applied to the drug product(s) [This is commonly referred to as the approved master label], the date and signature of the individual responsible for the preparation of all required records, and the signature of a second person designated as the quality control individual who independently checked and dated these records.

BATCH PRODUCTION AND CONTROL RECORDS

Section 211.188

Batch production records must document all significant steps performed during the filling operation, such as the prefill inspections for the high pressure cylinders and cryogenic vessels, the number and size cylinders filled, the filling inspections, the post fill checks, analytical test results, the lot number assigned, the final temperature and pressure results, the initials of the pumper/analyst, the signature of the individual who checked the entries for accuracy and completeness, the dates the above procedures were performed, etc.

Batch production records must be reviewed prior to the release of the finished drug product.

It is unacceptable to use a single entry to indicate that all of the significant steps have been performed, or to use a check mark , 'x' or other symbol, where the actual value is required to be recorded such as the temperature/pressure readings, purity and identity results, etc. A firm should amend its batch production record to provide for an item by item entry. [See the attached batch production record example for high pressure cylinder filling for details.]

A batch production record is a control record documenting that all of the required operations were performed during a comprehensive or elaborate manufacturing procedure or process. In fact, a batch production record is a snapshot of the actual production at the time of its performance, therefore, each significant steps should be documented as the operation is completed.

PRODUCTION RECORD REVIEW

Section 211.192

All drug product production and control records, including those for packaging and labeling, must be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is release or distributed.

Any unexplained discrepancy or failure of a batch to meet any of the specifications shall be thoroughly investigated whether or not the batch has been distributed. A written record of the investigation shall be made and shall include the conclusions and follow-up. This would include any test results that are outside of the established limits.

LABORATORY RECORDS

Section 211.194

Laboratory records should include complete data derived from all tests necessary to assure compliance with established specifications and standards. This would include all graphs, charts, etc., all calculations performed in connection with a test especially for mixtures or blends, the initials or signature of the analyst, and the initials or signature of a second individual showing that the original records have been reviewed and are in compliance with all established standards.

When using a handheld oxygen analyzer to perform an identity test, the actual value obtained must be recorded. A firm must establish written procedures addressing the acceptable range which would be a factor of the accuracy of the analyzer. For example, if the oxygen analyzer has a 2.0% accuracy, then the range would be between 97.0% and 102.0%.

CERTIFICATE OF ANALYSIS (COA) - Incoming Liquid Supply

All incoming supplies of liquid medical grade product should be accompanied by a COA containing at a minimum the following information:

- 1) Supplier's name and complete address

- 2) Name of the Product, i.e., Oxygen U.S.P.; Carbon Dioxide U.S.P.; Nitrogen NF; Nitrous Oxide U.S.P.; Helium U.S.P.; and Medical Air U.S.P.

NOTE: The following statement "Conforms to U.S.P./NF Requirements" would not be acceptable.

- 3) An Air Liquefaction Statement, where appropriate

- 4) A Lot Number or other unique identification number
- 5) The Actual Analytical results for full U.S.P. monograph testing.

NOTE: The following statement "Meets the minimum purity of 99.5%, etc. is not acceptable."

- 6) The Test Method used to perform the analysis. The statements "Meets U.S.P. specifications" or is "Tested via Servomex" are not acceptable, since the specific model number has not been provided.
- 7) Supplier's signature and the date, and
- 8) If applicable, the signature of the HCC employee witnessing the testing at the supplier.

DISTRIBUTION RECORDS

Section 211.196

Records should contain the name and strength of the product, what the patient received, i.e., D, E cylinders, cryogenic home vessel, etc., the name and address of the consignee, customer, or patient, and the date and quantity shipped.

A firm should establish a system whereby the distribution of each lot of a medical gas can be determined in the event that a recall becomes necessary. Please note that the distribution records for compressed medical gas products are not required to contain lot or control numbers in accordance with this section.

However, section 211.150 requires that written procedures describing a system by which the distribution of each lot of drug product can be readily recalled.

COMPLAINT FILES

Section 211.198

Written procedures must be established and followed describing the handling of all written and oral complaints, a detailed written record of each complaint, any investigation conducted, and where an investigation is conducted. The written record shall include the findings of the investigation, any follow-up required, and documentation of the review by the quality control unit.

These procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA in accordance with Section 310.305.

Section 310.305 requires any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible but within 15 working days of initial receipt of the information. This would include any problems associated with the drug product, the valve, the high pressure cylinder, etc.

In addition, according to Section 314.80, which became effective April 6, 1998, an Adverse Drug Experience Report must be filed for any adverse event associated with the use of a drug in humans, whether or not considered drug related, including: problems associated with the valve, the valve seal material, ejection of valve stems, the container whether it be a high pressure cylinder or a cryogenic vessel, any deaths or injuries resulting from mix-ups, contaminations, etc., changing outlets which result in either death or injury, etc.

RETURNED DRUG PRODUCTS

Section 211.204

Due to the sophistication of techniques required to requalify returned drug products for use, FDA recommends all high pressure cylinders transferred from the care, custody, or control of the manufacturer be vented to the atmosphere. Even if the drug product has not been used, and the seal is intact. Under no circumstances, should the cylinders be redistributed to patients until all required prefill, fill, and post fill operations and finished product testing has been completed.

DRUG PRODUCT SALVAGING

Section 211.208

Products failing to meet U.S.P. specifications are required to be vented. Repeated testing, in order to pass a drug product is not allowed. Once a failing result has been obtained all testing must cease until a thorough investigation has been performed, completed, documented, and reviewed by the quality control unit, as to why a failing result occurred. This must be covered in a firm's written procedures.

AIR SEPARATION PLANTS or UNITS

Air separation plants or units (ASU) take atmospheric air and through a purification process of cleaning, compressing, and cooling, separate the air into the constituent gases, oxygen, nitrogen, and argon. ASUs are highly computerized, and have very few employees in attendance during operations, which is usually 24 hours a day, 7 days a week. Therefore, process validation, and especially validation of computerized processes, is essential to ensure proper functioning of the process, and the product quality.

The requirement for computerized process validation has been around since the last major revision to the current good manufacturing practice regulations which occurred on September 29, 1978. Process validation was addressed in FDA's 1987 Guideline on General Principles of Process Validation, and much has been written about this subject in the industry trade press. Therefore, both the requirements and the agency's expectations have been around for some time.

For non-validated ASUs that have been in operation, i.e., shipping medical grade product, firms may apply, as a remedial measure, retrospective validation. (Product shipped from such

unvalidated processes would be adulterated in the CGMP context.) As addressed in the 1987 validation guideline, a key principle in retrospective validation is that current operations are the same as past operations with respect to product specifications, the range of operating conditions, and equipment (ranges and changes).

It is important that all changes and controls implemented since the original distribution of medical grade product in the retrospective period have been sufficiently documented. Otherwise, retrospective validation would not be scientifically sound, and older ASUs would need prospective validation, as would a new ASU that has not distributed medical grade product.

An ASU must comply with all appropriate CGMPs, some of which are but not limited to:

- * process validation including computer systems validation
- * establish a Quality Control Unit and written procedures
- * training
- * in process testing

- * lot numbering
- * written procedures
- * calibration of analytical equipment
- * testing finished product
 - U.S.P. equivalent testing methodology
 - testing residual, i.e., tankers, trailers, etc. prior to filling
- * validation of non-U.S.P. testing methodology
- * batch production records
- * documentation
- * certificate of analysis provided with each load, and all medical product designated as U.S.P./NF, if sold to a medical drug filler.

Another area of particular concern which has come to our attention is the lack of QCU sign off on all records, prior to release of a shipment, especially at locations that have few to no employees on site during the nighttime hours. A firm MUST not allow third party truck drivers to sign off as their QCU representative. This would amount to falsification of official records.

HEALTH CARE FACILITIES INSTALLATIONS

[Involves installation of a storage tank, usually at a hospitals, nursing homes, etc.]

In 1996, 11 tragic deaths occurred in a Temple, Texas hospital during the installation of an oxygen storage tank. The hose used to connect a temporary oxygen supply to the hospital's oxygen system was inadequately purged of a toxic cleaning solution, and the installing firm failed to detect the toxic contaminant. Our investigation of the incident revealed the firm had failed to comply with the CGMPs for this type of operation. In fact, we later determined that this was an industry-wide failure.

The CGMPs apply to 1) the initial installation operation, ending at the point where the piping enters the building, and 2) anytime the system is compromised and exposed to a possible contaminant or impurity, such as new valve installation, new piping, etc. It is a firm's

responsibility to determine the critical points and areas of their operation where problems or contamination may occur and to assure compliance.

Therefore, any firm involved in this operation must comply with all appropriate CGMPs, some of which are but not limited to:

- * establish a Quality Control Unit and written procedures
- * training of the service technicians, etc.
- * qualifying equipment for medical use
- * vendor/supplier audits of contracted cleaning firm(s) and written agreements
- * detailed written procedures
- * calibration of testing analyzers
- * finished product testing prior to introduction of the drug product into the hospital system
- * U.S.P. equivalent testing methodology
- * batch production records
- * certificate of analysis provided to the receiving facility with each delivery
- *documentation.

If a supplier or shipper contracts a third party to install a health care facility storage tank, it would be the supplier or shippers responsibility to determine whether the system has been installed in accordance with the CGMPs, prior to introducing the medical gas. This determination should be fully documented.

Please note each installation is required to comply with the National Fire Protection Associations requirements outlined in NFPA 99 and 50, in order to assure proper installation.

CARBON DIOXIDE MANUFACTURERS & WHOLESALE DISTRIBUTORS

Carbon dioxide manufacturing facilities generally receive carbon dioxide feedgas as co-product from associated industries. They provide process purification techniques and controls to eliminate or minimize contaminants to safe and effective levels while raising the carbon dioxide purity to acceptable levels.

They are expected to perform process validation including computer validation and comply with the CGMPs. It is essential that the firm have a written guarantee with the raw material

manufacturer to be notified of any changes to the production process or to the raw material. Another vital issue is the initial fingerprinting or characterization of the incoming "raw material" for any contaminants or impurities that could affect the finished drug product.

Therefore, all CO₂ manufacturers must comply with all appropriate CGMPs, some of which are but not limited to:

- * process validation including computer systems validation
- * raw material supplier agreements
- * raw material or stream fingerprinting or characterization
- * establish a Quality Control Unit and written procedures
- * training
- * in process testing
- * lot numbering
- * written procedures
- * calibration of analytical equipment
- * testing finished product
 - U.S.P. equivalent testing methodology
 - testing residual, i.e., tankers, trailers, etc. prior to filling
- * batch production records
- * documentation.

Finally, the product must be labeled Carbon Dioxide U.S.P.

All shippers, wholesale distributors, jobbers, transporters, etc. that fill into or from rail cars, storage tanks, trailers, vessels, etc. would be required to register and list, comply with the appropriate CGMPs, and be inspected.

EMERGENCY MEDICAL SERVICES (EMS)

EMS, i.e., fire departments, ambulance companies, rescue squads, etc. are defined as the following:

- 1) they are usually state government affiliated emergency services,***
- 2) they transfill Oxygen U.S.P. for their own use only. No other gases may be filled on site,***

3) they administer Oxygen U.S.P. to patients, victims, etc. in an emergency situation, and

4) they charge no specific fee for the administration of Oxygen U.S.P. nor do they receive any reimbursement from Medicare or Medicaid.

At the current time, we are not requiring EMS to register or list with FDA as long as the following minimum requirements are implemented: a) establish written procedures covering all operations including distribution within the organization, recalls, labeling, training, etc.; and b) establish records documenting the above. For specific details, please refer to the previously discussed sections of the CGMPs.

CAUTION: Any EMS failing to comply with (a) and (b) above, would be subject to the full CGMP requirements and would be required to register and list with the agency, and will be inspected.

GAS TO GAS ADAPTERS

The use of gas to gas adapters to circumvent the specific CGA valves and connections associated with a specific medical gas is a very dangerous practice. There have been mix-ups and contamination that have occurred in the past due to the use of adapters which have resulted in deaths and serious injury.

Adapters which only reduce or expand the connection size for a specific medical gas while still maintaining the proper connection system may be used. However, this practice must be defined in a firm's SOPs.

For the filling of mixtures, adapters may be used, however, written procedures detailing a system of checks should be in place to prevent mix-ups or contamination, and these should be documented. The adapters are required to be under security with limited access.

What are the possible consequences of not complying with the CGMPs?

Manufacturers report that each year there are returned to them supposedly empty cylinders that contain either a gas other than that originally shipped or a foreign odor. Some of these contaminating gases may be flammable, and intermixing a flammable and an oxidizing gas may cause a serious explosion.

On May 24, 1983, a large welding supply company in the southeast, delivered and connected a VGL thought to contain medical oxygen to a local hospital. During the course of the evening, the product was administered to a premature infant, a 46 year old male, and a 27 year old female in three different areas of the hospital and all three died. Analysis of the gas found that the alleged oxygen was in fact argon. To further complicate matters, the VGL was partially labeled "Liquid O," had a second label on the other side which read argon, and the fill line had an argon fitting while the discharge line had an oxygen fitting.

In 1987, a large welding supply company located in the northeast, jury-rigged four oxygen cylinders which were painted gray, and placed CO₂ into these cylinders. However, the cylinders bore a correctly Oxygen U.S.P. label, and had the correct CGA 540 oxygen valve.

In addition, the firm failed to have written procedures covering the filling and handling of different colored cylinders. Four (4) of the cylinders were subsequently sent to a hospital and administered to two patients undergoing surgery. One patient's death was attributed to carbon dioxide exposure while the other patient was seriously injured.

On December 20, 1993, a home care company located in the northeast and filling liquid oxygen only, had it's employee go to their supplier to pick up a GP-45 of Oxygen U.S.P. The supplier's employees were too busy to accompany the home care company's employee to the loading dock, so they authorized the employee to go to the loading dock and select one of the GP-45s. Unfortunately, the employee who was inadequately trained, selected a GP-45 of argon, instead of Oxygen U.S.P. Although a certificate of analysis was provided, no testing was performed and the labeling was not examined.

The employee loaded the vessel into the van and went to three (3) patients homes to fill their vessels, however, the employee encountered a problem. When he went to fill the cryogenic home vessels, the discharge line was not compatible with the vessels fittings. So he took a fitting from a spent oxygen vessel and installed it on the GP-45, he could now fill the patients cryogenic vessels with the deadly product. Luckily, the next day, the employee became aware of the argon mix-up and retrieved all 3 vessels with no injuries. Fortunately, these three patients were not dependent on high inspired oxygen concentrations.

In March 1996, we received a report of eleven deaths associated with contaminated oxygen being delivered to a VA hospital in the southwest. According to the report, a large storage tank was being replaced, and a temporary 500 gallon cryogenic vessel was brought in and connected to the hospital's main oxygen system via a 50 foot hose. A subsequent analysis of the 50 foot hose tested positive for the presence of trichloroethylene, a standard cleaning chemical, but very toxic to humans.

On July 15, 1996, in Fredericksburg, Virginia, the former president of a medical oxygen facility pleaded guilty to making false statements to the Food and Drug Administration about his company's testing and filling of medical oxygen. During the February inspection, the president was informed of significant CGMP violations occurring at the firm. In March, he agreed to recall the adulterated drug product and informed FDA that he had done so. However, FDA later discovered that the firm in fact did not recall the adulterated product. The president was sentenced to serve one year and one day in prison, to perform 200 hours of community service, and to pay a \$30,000 fine for making false statements to FDA.

On December 2, 1996, a children's home located in New York reported adverse reactions experienced by nine patients due to the inhalation of carbon dioxide, instead of oxygen. Our investigation found the firm supplying the medical grade product had included a cryogenic vessel of industrial grade carbon dioxide. An employee of the home went to attach a cryogenic vessel of Oxygen U.S.P. and unfortunately selected the carbon dioxide vessel, and he failed to examine the label. He noted the fittings on the carbon dioxide vessel weren't compatible with the connector on their oxygen system, so he removed an oxygen fitting from an empty oxygen vessel and installed it on the carbon dioxide vessel. He then introduced the carbon dioxide into the oxygen system. Two of the patients were injured critically, four experienced varying stages of respiratory distress, and three were not affected.

In addition, the deliver driver received no CGMP training, and the truck had inadequate areas of separation of the medical grade from the industrial grade product.

In October 1997, we received a second report similar to the New York children's home. However, this time there was a report of a death occurring at a Nebraska hospital due to the inhalation of argon. The hospital received a shipment of Oxygen U.S.P. in cryogenic vessels, and included in the delivery was a cryogenic vessel of argon. The hospital was running low on oxygen and sent a maintenance man to connect a new oxygen supply vessel to their system. He selected the argon vessel, failed to examine the label, and was unable to connect the vessel to the oxygen system. He removed the fitting from an empty oxygen vessel, installed it on the argon vessel, and was then able to connect the deadly product to the oxygen system. Argon was administered to a patient who was undergoing minor surgery, and died.

Once again, our investigation found the delivery driver was inadequately trained on the CGMPs, and the truck had inadequate areas of separation of the medical grade product from the industrial grade product.

On April 22, 1998, we received our third report from a hospital in 3 years. A hospital located in Idaho discovered a large cryogenic vessel of industrial grade nitrogen had been connected by the supply firm's driver to their oxygen system which supplied the operating rooms, labor and

delivery rooms, and the emergency room. The delivery driver was an inadequately trained college student who had failed the firm's driver certification test. When the driver was unable to connect the incompatible nitrogen vessel outlet fitting, he disconnected the nitrogen fitting and replaced it with the appropriate oxygen fitting so that it could be connected to the oxygen system. Unfortunately, two deaths are associated with the administration of the toxic industrial product.

On October 5, 1999, a durable medical equipment supply firm located in Tennessee which was subject to one of FDA's seizure actions, and its president were found in CIVIL CONTEMPT for moving and tampering with items that were seized by the U.S. Marshal's Office.

GLOSSARY

The following definitions are provided to assist the reader in using this document.

- 1) **Cascading** - This is a cylinder filling system consisting of a supply cylinder unit, [commonly referred to as a "Bank"] such as a group of H or K sized cylinders, a receiving cylinder unit, such as a filling manifold, and a vacuum evacuation unit. The first (lowest pressure) supply cylinder's valve is opened and the gas flows into the smaller cylinder(s) until equilibrium is reached. This continues until the desired pressure is reached in the smaller cylinder(s). Individual cylinders in the bank are replaced sequentially as their respective pressures are diminished to levels that are ineffective for the transfer operation. When this occurs, the first cylinder's valve will be closed and the second supply cylinder's valve will be opened allowing the gas to flow into the smaller cylinder(s). This continues until the smaller cylinder(s) is filled.
- 2) **Certificate of Analysis** (COA) is a single document usually provided with each shipment of incoming liquid drug product that undergoes further processing, i.e., filling, transfilling, etc. A COA should contain all of the required information that would allow the receiving firm to determine if the drug product is acceptable. This document may come in any form, such as a letter of conformance, a bill of lading, an invoice, etc. and does not have to be identified as a "COA" but must contain all of the required information. Otherwise, it would be deemed unacceptable and further testing may be required.
- 3) **Cryogenic home vessels** (CHV) are vessels designed to hold liquid oxygen at a patient's home.
- 4) **Distributor** is a firm that receives fully labeled, finished drug product either liquid in large cryogenic vessels, i.e., VGLs/GPs, etc. and/or high pressure cylinders and

does not manipulate the product nor the labeling in anyway. Therefore, they would not be required to register.

However, a distributor should establish and follow recall, complaint and distribution procedures capable of determining the traceability of the drug product.

- 5) **Handheld oxygen analyzers** are oxygen analyzers which may be held in ones hand or may be stationary, that operate on the fuel, electrochemical, galvanic, or polarographic cell principle. When properly calibrated, these analyzers may provide a specific oxygen identification test result only, since they fail to possess the required U.S.P. accuracy. These analyzers must be calibrated with a certified calibration standard.
- 6) **Home Care Company/Home Respiratory Care Company (HCC)** usually sell durable medical equipment and supply liquid oxygen to patients are their home. These firms may also fill via cascading high pressure cylinders as backups for their oxygen concentrators.
- 7) **Large cryogenic vessels or Dewars** are containers used to hold a low pressure, liquid product at a very low temperature, and are similar in design to that of an insulated thermos bottle with a vacuum between the inner and outer container. These vessels are portable such as VGLs (Vertical Gas Liquid), GPs (Gas Pack), or PLCs (Portable Liquid Container). This does not pertain to tankers, or vessels permanently mounted in a vehicle, such as HL119s, MDX 60s, 80s, 119s, etc.
- 8) **Manufacturer** is any individual or firm filling liquid to liquid, liquid to gas, and/or gas to gas. As a manufacturer, a firm is required to register and list with the agency and to comply with the CGMPs. In addition, a firm should check with its state to determine if there are any state requirements, such as licensing that a firm may need to comply with.
- 9) **Oxygen for Environmental Use** means oxygen meeting the U.S.P. specifications and used to support life artificially in environments which are normally deficient. This definition includes, but is not limited to, space and space simulation capsules, deep submersibles, scuba, etc. It specifically excludes oxygen used in chambers or devices for the medical therapeutic treatment of man or animal.
- 10) **Oxygen for Industrial Use** means oxygen not intended for inhalation or therapeutic treatment of man or animal.

- 11) **Oxygen for Aircraft Use [Aviators Breathing Oxygen]** means oxygen in fixed or portable oxygen containers or systems intended for commercial or private aircraft use, meeting the U.S.P. specifications and having the special moisture and/or other limiting characteristics required for aviators breathing oxygen (ABO). ABO may not be used for recreational inhalation or medical therapeutic treatment of man or animal.
- 12) **Process Validation** as defined in the Guideline on General Principles of Process Validation, May 1987, is establishing documented evidence which provides a high degree of assurance a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.
- 13) **Storage Tank or Stand Tank** is a large cryogenic stationary holding tank with a capacity of anywhere from several thousand to several million of gallons/liters of a liquid product. These are always located on the outside of a facility.
- 14) **Uninterrupted filling sequence** is a single, continuous filling sequence with no breaks or shut- downs occurring during the filling and provided the same personnel, equipment, and lot of component are used. If the filling sequence is interrupted then additional testing is required.

This procedure does not apply to the filling of high pressure cylinders on a multiple outlet manifold or rack.

- 15) United States Pharmacopeia/National Formulary (U.S.P./NF) is a reference of a select list of articles in the form of a monograph. Included in each monograph are the standards for determining the identity, strength, quality, and purity of the articles. Please note each individual monograph does not contain all contaminants or impurities that may be present. Refer to the General Notices under U.S.P. Monograph for details. The current edition is U.S.P. 24.

FRESH AIR '2000' CHANGES

- 1) Page 7, Equipment calibration frequency
- 2) Page 11, Odor testing unpressurized cylinders
- 3) Page 17, Out of Specification Test Results

4) Page 20, Portable or Add-On Racks validation

5) Page 27, Records - lack of documentation of significant steps

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