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**A Discussion on**

**Regulatory Issues & Requirements**

**Related to**

**Bulk Distribution of Medical Gases**

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## **I) Introduction**

The processes, equipment, and personnel associated with the delivery of bulk cryogenic liquid medical gases are all subject to FDA requirements and the regulations in Title 21 of the Code of Federal Regulations. Standard industry practice is to utilize the same equipment for deliveries to medical and industrial customers on the same delivery run. The US Food and Drug Administration (FDA) permit this as an acceptable practice, provided firms observe key provisions and requirements, some of which are specific to cryogenic deliveries. This paper is an overview of applicable FDA requirements, industry consensus standards, and current practices, and can serve as a general outline for firms seeking to establish an FDA compliance program for bulk deliveries of medical gases. This paper focuses on the requirements for Oxygen USP and Nitrogen NF, which are the predominant bulk medical gases sold today. For additional information regarding specific points raised in this document, or other medical gases, contact Chart Industries, or B&R Compliance Associates.

## **II) Background**

Nearly all US bulk gas manufacturing facilities are FDA registered, and produce medical gases. Therefore, the quality attributes of medical and industrial gases delivered from these ASU facilities are the same. The distinction between the two grades of gas is the paperwork which documents the manufacturing and delivery processes of medical products, not the manufacturing processes, or the purity of the gases themselves. Contrary to a persistent industry urban legend, dedication of delivery equipment to medical service is not a requirement in today's regulatory environment, and we do not anticipate this changing in the foreseeable future. In order to keep the bulk delivery process as efficient as possible, firms distribute bulk industrial and medical grade gases using the same delivery equipment, which is entirely acceptable, provided the delivery firm faithfully adheres to some specific technical, procedural, and documentation requirements. Any firm today that may be operating a dedicated medical fleet is doing so based entirely on their business portfolio, not any regulatory requirement.

While there are technical differences between the different micro bulk systems, as well as between micro bulk and traditional bulk tankers, from an FDA regulatory standpoint all of these systems face the same basic set of requirements. FDA would expect any specific technical or regulatory issues to be included and appropriately accommodated & managed through the firm's compliance program.

## **III) Qualification of Product & Manufacturers**

Product delivered and sold as medical grade product must have originally been manufactured as medical product. Since there are no drug product labels on bulk delivery units or storage vessels, this is typically documented through a certificate of analysis (COA) that accompanies the product. The COA provides the necessary evidence a delivery is USP / NF product. It is absolutely un-acceptable to fill a delivery unit with industrial grade product, test the product in the delivery unit, and then sell it as medical grade. The paperwork pedigree of any bulk medical gases must ultimately be able to directly trace its lineage back to the Air Separation Unit that produced it.

FDA defines the filling of delivery units with medical gases as drug manufacturing. ASU's that ship medical grade product, as well as firms that fill medical delivery units from a bulk storage vessel at their site, must register with FDA as a drug manufacturer. They will also need to comply with

applicable state registration requirements for both pharmaceutical manufacturing and wholesale distribution of drugs in each of the states they do business in. These requirements for licensing and registration are no different than what is required for filling high pressure cylinders.

#### **IV) Qualification of Delivery Units**

Determining if a delivery unit is in medical or industrial service is predominantly a function of its paperwork pedigree. Units that have industrial grade documentation are considered in industrial service. Conversely, units with USP / NF grade documentation are in medical service. This remains true even if a unit in medical service only makes deliveries to industrial customers. Industrial service units moving into medical service must first go through a qualification process. The same holds true for new delivery units, unless the manufacturer can provide appropriate documentation showing the unit is already qualified for medical service. Some of the key steps in this medical qualification process involve pressurizing and venting the unit an appropriate number of times, performing testing, and documenting each step of the whole process. You cannot simply perform testing on an industrial unit and call it medical; there must be some activity which cleans/qualifies the unit. A more recent enforcement trend is that FDA has begun expecting firms to validate this change of grade process. The gases industry has recently addressed change of grade in bulk delivery units by developing a general set of requirements in CGA publication M-14 *Bulk Trailer Change of Grade*. When loading at an ASU it is common practice to verify a unit's medical grade pedigree before loading medical product, and FDA would expect the same to hold true for firms that load units from a bulk storage tank or a bulk cryogenic tanker on their property.

Once medically qualified a delivery unit is considered in that service provided it is re-loaded with medical product, and the unit's documented medical pedigree remains un-broken. The exception to this is if a "qualifying event" occurs. A couple examples of qualifying events include:

- A unit in medical service experienced a total loss of pressure due to a bursting disk failure, and the contents are potentially exposed to atmospheric air.
- There was a backflow of product into the delivery unit from the bulk tank being filled.
- A two hose delivery system is used, thereby allowing product from the customer vessel to be returned to the delivery unit. This is most common in CO<sub>2</sub> and N<sub>2</sub>O deliveries.
- The unit was loaded at a facility not registered with the FDA. This could be either an ASU or a distributor location with a bulk vessel used to load delivery units.

In each of these instances the delivery unit would likely need to undergo the re-qualification process prior to being re-loaded with medical grade product.

#### **V) Filling & Delivery Operations**

Prior to loading a delivery unit already in medical service a pre-fill analysis must be performed on the residual product in the delivery vessel. Units that fail pre-fill analysis cannot be filled with medical grade product without going through the qualification process and then passing another pre-fill analysis. It is un-acceptable to re-test failing units until they pass the pre-fill analysis. Once filled, each unit must be tested for all required USP / NF tests, and each unit given a unique lot number for that load of product. In some areas of the country firms have their bulk supplier fill their delivery units directly from the bulk tanker at the same time they fill their bulk supply vessel. This is acceptable,

provided the firms procedures adequately ensure a pre-fill analysis is performed, and the delivery units are held in quarantine until they are analyzed and released by the QC Unit for distribution. Most firms elect to utilize the same procedures for both medical and industrial, deliveries, opting to utilize one process for both types of deliveries; however, typically the documentation required for medical loads is not kept for industrial deliveries. There are some key provisions associated with making medical product deliveries. Drivers must have documented training, including basic cGMP training. All medical delivery processes must be performed in accordance with written standard operating procedures. All procedures and specifications must be approved by the QC Unit, and the key steps of the loading and delivery processes must be documented. The most important provision is maintaining the delivery unit's medical pedigree by preventing any potential backflow from the customer vessel into the delivery unit. FDA's position on backflow is that even a de minimis amount is un-acceptable, and breaks the delivery unit's medical pedigree. Across the industry there is a wide variety of backflow prevention practices, ranging from engineering controls such as installing a validated spring loaded check valve in the delivery pump outlet line, to procedure based controls such as having the driver monitor and record delivery unit and vessel pressures, thereby documenting no backflow occurred from the customer vessel during the delivery. A final issue concerns the delivery hose itself. Hoses that are not kept capped and protected from the elements between deliveries can potentially introduce significant levels of contaminants into the customer vessel during product deliveries. The delivery firms procedures should stipulate that hose caps must be used religiously between deliveries, and driver training should reinforce that requirement.

#### **VI) Multiple Use of Delivery Units**

Under current FDA guidelines it is acceptable for delivery units to service industrial and medical customers during the same delivery run. Provided the unit only makes single hose deliveries, and no product is returned from the customer vessel, the order of the delivery is not an issue. Firms can schedule medical and industrial deliveries in the most logistically efficient order. If the unit loses its medical pedigree in the middle of a delivery run due to a qualifying event, it can still make industrial deliveries until it returns and goes back through the qualifying process prior to re-loading. The basic philosophy governing delivery unit multiple use, is that this process is acceptable as long as the unit is only loaded with medically qualified product, the unit's medical product pedigree is maintained, and that all applicable cGMP requirements are observed when making both industrial and medical deliveries. The final and key proviso to operating delivery units in the multiple use mode is preventing backflow into the delivery unit from the customer vessels.

#### **VII) Documentation Requirements**

In pharmaceutical manufacturing, the documentation processes and the diligence a company applies to them are essential to ensuring compliance to FDA requirements. Some of the issues specific to bulk delivery units, which firms need to focus on include:

- Documentation of the key steps in the delivery unit re-loading process
- Documentation of the key steps in the customer delivery process
- Documentation of delivery unit qualification activities

- Documentation of delivery unit maintenance activities – both preventative & repairs
- Maintenance of the delivery unit's medical paperwork pedigree

Customers receiving medical product must be provided a certificate of analysis for each load/delivery of product. The bulk product COA, like the drug product label applied to cylinders, serves to identify the product and its quality attributes. When making night time deliveries it is common for the driver to leave the COA document in a box or container near the vessel, rather than give it directly to the customer. While not mandatory, many companies want a customer signature on the delivery paperwork as confirmation that the delivery was made correctly.

One area where companies have run afoul of FDA regulations is to permit the delivery unit once filled to leave the facility before the documentation has been reviewed and approved by the QC Unit. Firms that permit this practice are violating one of FDA's cardinal rules and risk severe FDA sanctions on their business. Finally, many firms are moving to remote release of bulk product, especially in delivery operations that run 24/7. There are a number of key requirements involved in setting up a program to perform the remote release of product, but since virtually every operation is different, it is best to discuss your specific issues with a compliance expert to develop a customized solution for your operation.

#### **VIII) References**

The following is a list of Consensus Standards and other resources which can provide valuable additional information and support on this topic.

##### **Standards**

- Compressed Gas Association Publications – [www.cganet.com](http://www.cganet.com)
  - CGA M-1 *Guide for Medical Gas Supply Systems at Consumer Sites* – Edition 2 - April 2007
  - CGA M-3 *Guide for the Manufacturer of Bulk Medical Gases* – Edition 2 – July 2007
  - CGA M-14 *Bulk Trailer Change of Grade* – Edition 1 – August 2009
- National Fire Protection Association – [www.nfpa.org](http://www.nfpa.org)
  - NFPA 99 - Health Care Facilities – 2005 Edition

##### **Consulting Resources**

- Bob Sutter – B&R Compliance Associates LLC – (610) 868-7183 [www.brcompliance.com](http://www.brcompliance.com)
- Matt Martineau – Chart Inc. – (952) 758-8586 [www.chart-ind.com](http://www.chart-ind.com)