



by Ron Ball

Qualifying Cylinders and Valves for Medical Service

The key requirements in procuring and managing medical gas cylinders and valves in compliance with the FDA are gaining acceptance by customers and manufacturers alike.

Qualifying cylinders and valves for medical service is a critical element of an effective FDA compliance program. Historically, many of the root causes of con-taminated medical gases that have made their way into the supply chain can be directly traced to improper qualification of items used to hold medical gases, including cylinders and valves. This article will examine some of the key requirements in procuring and managing medical gas cylinders and valves in compliance with FDA requirements, including the new integrated valve units, which are gaining acceptance by customers and manufacturers alike.

FDA regulations do not specifically address requirements for medical gas cylinders and valves. In FDA terminology medical, gas cylinders and valves are known as containers and closures. The regulations governing drug product containers and closures are found in 21 CFR, Subpart E – Control of Components and Drugs Product Containers and Closures – §211.80 – §211.94.

These requirements specify that containers “. . . shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug” The same procedures further specify that all activities governing receipt, identification, storage, handling,

sampling, testing, and approval / rejection be performed in accordance with detailed written standard operating procedures, or SOPs.

Medical Gas Containers Are Unique

When compared to drug containers and closures in the pharmaceutical industry, medical gas containers and closures are unique. There are no other container closure systems used to hold finished pharmaceuticals, which are routinely re-used or refilled. When was the last time you went to your local pharmacy for a prescription refill, and the pharmacist simply put more pills into the same bottle? The medical gas industry would not exist as we know it today without this unique accommodation of the regulations. However, this accommodation for medical gas containers and closures in the cGMP requirements also creates some special obligations on the part of manufacturers to ensure that cylinders and valves are properly qualified for medical service each time they are used.

When specifying and purchasing cylinders and valves for medical gas service, it is important to ensure that the materials of construction are compatible with the gas service and its intended use. For high pressure, cylinders this requirement typically focuses on ensuring that valve seats and packing materials are compatible with the specified gas service.

While oxygen service is typically the most demanding in terms of ensuring materials compatibility, there are some materials that are unacceptable for carbon dioxide service. In the medical gas industry, valve manufacturers take the appropriate steps to ensure materials compatibility, and medical gas firms accept the documentation provided by their valve manufacturer / supplier. This is an acceptable practice—with one proviso. FDA guidance documents that cover container closures stipulate that the drug manufacturer and the container / closure fabricator share responsibility for the integrity and quality of the container / closure. The FDA expects that firms will periodically audit their supplier to verify that the supplier is in conformance with those FDA procedures that ensure product quality. The FDA is well aware that despite the valve and cylinder suppliers manufacture’s adherence to a common standard, such as CGA or ISO, individual company practices can impose a significant positive or negative impact on the quality of finished products. The FDA desires that medical gas firms assure for themselves that their suppliers live up to the standards and procedures they have established to guarantee the quality of their products. In the medical gas industry, it is also very important to ensure that containers and closures are cleaned in accordance

with use for medical service. The cleaning process must be such that no residual contamination remains, which could alter the identity or quality of the medical gas. This includes any residual odor. We recommend that all medical cylinders and valves be cleaned for oxygen service, regardless of the intended gas service. Cleaning for medical service is also a concern for cylinders sent out for re-testing. We, along with FDA, recommend that firms that re-test cylinders hydrostatically use water that meets drinking water standards. We have personally observed re-test water in use that was virtually black and had an offensive odor because it had been recycled many times. In a situation such as this, it would be difficult to justify to an FDA inspector that these cylinders were acceptable for medical service. Another key consideration is to ensure that contamination is avoided while the cylinders are open and the interior surfaces are exposed. Reliable hydro test firms use some approved method to cap open cylinders in order to protect cylinder valves from ambient sources of dirt and contamination until the valve is re-inserted. We recommend medical gas manufacturers periodically audit their re-test vendors to verify the validity of any cleaning processes used, and check how cylinders are protected during the test process.

IVU Technology Grows Rapidly

A new technology entering the medical gases industry in increasing numbers is the **integrated valve and regulator unit (IVU)**. Most of these are now listed with the FDA as medical devices. They are manufactured by FDA-registered medical device manufacturers. While IVUs are listed only as class I devices, this listing imposes some additional requirements for container and closure qualification.

When a reconditioned IVU is delivered pre-mated to a cylinder, that cylinder must be held in quarantine. The same requirement applies if only the IVU itself is received and your firm mates the IVU to a cylinder. Before any IVU/cylinder unit can be put into use, it must be inspected to establish that it meets acceptance criteria and specifications your company established when that unit was ordered. Acceptance criteria and specifications should include the requirement that valve connections

conform to CGA standards, that the unit has the flow rate specifications requested, that it includes a residual pressure cylinder valve (if requested), and that the manufacturer has included the appropriate paperwork to document the shipment. This same inspection should also ensure that the unit is not damaged, or that it did not become contaminated during shipment. This inspection should be performed by someone with the appropriate knowledge and training to conduct this procedure. Once the inspections are completed, the documentation must be reviewed and approved by a member of your company's QC Unit, after which it can be released for use. Units should not be filled with medical gases until the QC Unit has released them from quarantine.

Re-filling Has Additional Requirements

Re-filling integrated valve units creates additional requirements. Most IVU manufacturers, as stipulated in their operations and maintenance documents, require periodic verification of flow rates. These requirements are part of the process that ensures the on-going qualification of a medical device, and ensures that the IVU continues to function in accordance with the system design parameters. CGA publication

E-7, section 7 specifies that flow rates of medical regulators shall be verified at a minimum of every five years. CGA E-7 also recommends that the unit be returned to the manufacturer for this inspection and calibration. As part of this process, firms must show that they have tracked and documented flow verification. We therefore, recommend that firms either log or otherwise document individual IVU unit serial numbers, or have some other method to individually identify each unit. Firms will also need to document these periodic inspections, along with the results, and this documentation should be reviewed and approved by the QC Unit.

We are finding that integrated valve units are very susceptible to damage in the field. Customers report a significant percentage of their fleet returns have a damaged cover or the valve assembly due to rough handling in the field or during shipment. Units that sustain damage that is more severe than a cracked housing, need to be inspected to ensure that they still meet their design performance specifications, including verification that outlet pressure and flow delivery rates meet

manufacturer requirements. This is very different from traditional cylinder valves, where the two-step leak test proscribed by FDA is sufficient to re-qualify the unit for medical service. A final word of advice on IVUs is to follow the manufacturer's instructions that cover maintenance and calibration. Some manufacturers have set intervals for flow rate verification, using a proprietary flow calibration device. Firms that ignore these recommendations are at risk during an FDA inspection, particularly since these are medical devices. The key element in ensuring that containers and closures meet and maintain acceptability for medical service is to establish an adequate set of standard operating procedures (SOP) and to follow your procedures. When adopting new technology it is equally important to re-visit your SOPs and ensure that they evolve to incorporate any new requirements.

For more information on qualifying medical cylinders and valves or medical gases in general contact Ron Ball at B&R Compliance Associates LLC (317) 297-8518 or visit B&R on the web at: www.brcompliance.com.



Integrated valve and regulator unit (IVU) on E Cylinder (left) and oxygen conserving regulator with CGA40870 connection (above). Photos courtesy Western Medical Gas Control Technology.