



by Ron Ball

# New Medical Gas Technologies and their Impact on Compliance Requirements

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While the medical gases industry is experiencing dynamic growth in both markets and new technologies, many producers have been reluctant to invest in capital equipment or adopt manufacturing and distribution processes that will enhance their productivity and profitability. Blame it on high costs and inertia. But more recently, signs of change have been perceived as medical gas manufacturers recognize that change is inevitable if they are to remain competitive in a rapidly evolving medical gas marketplace.

Capital investment and implementation of new methodologies, however, make up only part of the picture. Firms that are regulated by the FDA are well advised to ensure that new technologies and manufacturing methods adopted are in compliance with the latest regulations. Three developments currently in effect must be considered

## ***Electronic Records***

FDA 21 CFR Part 11, introduced in 1998, establishes requirements for electronic records and electronic signatures.

The potentially high cost of implementation, however, dissuaded many firms, both large and small, from adopting the new technologies that would permit implementation. These costs included cylinder tracking, paperless deliveries, and electronic record-keeping. During the past 18 months, the agency had been taking steps to modify the Part II requirements to reduce the dampening effect they were creating on the spread of electronic technologies in the drug industry. As a result, compliance expectations, as well as requirements, have been modified significantly.

Recent FDA actions have been focused on encouraging firms to adopt 21st century technologies that promote higher productivity, reduce errors that need to be corrected, and improve tracking of product deliveries and assets. From the FDA perspective, improving product traceability and reducing record-keeping errors are desirable steps that improve a firm's cGMP capabilities.

In the past, many gas producers intro-

duced electronic record-keeping, but only for their industrial customers. The medical side of their business continued with the traditional (paper) processes. This resulted in two different business processes being conducted within the same company—a situation that could lead to record-keeping errors. The companies with the two-process accounting system realized that if they went back and implemented electronic records for their medical business, they would have to redo much of the work necessary to make the system FDA compliant. This situation typically results when acceptable documentation commissioning is not developed and maintained at the time of initial system commissioning. Had that been done at the start, that documentation could have been used to (at least partially) satisfy FDA requirements.

Often, most of this activity, if planned and documented properly, can be used to meet FDA Part 11 requirements, making FDA compliance an incremental project expense. It is strongly recommend that firms planning to implement an electronic

record or signature technology carefully evaluate what it would take to comply with FDA requirements. It may be easier than you think if you build FDA compliance into the project, rather than attempt to add it on later.

When electronic technologies are implemented, the FDA recommends that risk assessments be used as the tool to evaluate the proposed project and business practices, and to help plan implementation of a compliant Part 11 technology. Firms can identify project areas that require a specific focus to achieve FDA compliance, and to plan accordingly. Numerous risk assessment methodologies and tools are available that allow firms to match the risk assessment process to the project's complexity. With the FDA's move toward risk based compliance strategies, developing the internal capability (or access to third-party resources) to conduct risk assessments as a decision tool is something every medical gas manufacturer needs to consider.

Validation is yet another reason firms have stayed away from electronic tech-

nologies in their medical operations. It is frequently viewed as too complex and too costly, and there is no doubt, under certain circumstances, that it will prove to be expensive. Very often, the activities a manufacturer undertakes to verify a system's accuracy and reliability of data, can be considered elements of the validation process. It is also often not necessary to validate an entire system—only the elements of a system that are utilized to capture or store a record required under 21 CFR. This is where a thorough risk assessment can help guide managers in making informed decisions that help them achieve compliance. Smaller firms may need third-party assistance in conducting risk assessments, or in setting up their validation protocols, but almost every medical firm today has the expertise needed to execute and document its own validation.

### *The Integrated Valve Unit (IVU)*

A second technology that is gaining broad acceptance in the medical gas industry is the integrated valve / flow-meter

/ regulator unit, or integrated valve unit (IVU). Available from a variety of manufacturers, with a variety of features, IVUs are becoming popular due largely to the increased convenience they offer customers. However, it appears that compliance with FDA regulations in some areas is lagging behind implementation of the technology. Some IVUs available in the market are Class I medical devices; the firms that make them are FDA registered medical device manufacturers.

Other units currently available are not medical devices. This is one instance in which FDA regulations can work to the manufacturer's advantage. Medical device firms are required to comply with FDA's Quality System Regulations (QSR). This means that they must meet certain compliance requirements for their operations, such as having SOPs, developing employee-training programs, maintaining product traceability, and having complaint and CAPA systems in place. It makes sense that the firms registered as device manufacturers (by virtue of having to meet FDA QSR regulations) have invested

## Title 21 Code of Federal Regulations (21 CFR Part 11) Electronic Records; Electronic Signatures

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### UPDATE:

- The Current Status of 21 CFR Part 11 Guidance is located under Regulations and Guidance at: <http://www.fda.gov/cder/gmp/index.htm> (see background: <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-4312.pdf>)
- [FDA Guidance Documents - A subject list of open dockets for guidance documents concerning 21 CFR Part 11.](#)
- [Public Meeting June 19-20, 2000 on Industry Experience Implementing Technical Provisions of 21 CFR Part 11, Federal Register \(FR\), February 22, 2000](#)
- [Enforcement Policy Compliance Policy Guide, FR, July 21, 1999](#)

### BACKGROUND:

- [Electronic Submissions to FDA Docket 92S0251 Contents](#)
- [Final Rule \(text file 76 pages\), FR, March 20, 1997](#)
- [Docket 92S0251 \(text file\) Established, FR Notice, March 20, 1997](#)
- [Side by Side Comparison of Proposed and Final Rules](#)
- [Proposed Rule, FR, August 31, 1994](#)
- [Advance Notice of Proposed Rulemaking \(text file\), FR, July 21, 1992](#)
- [FDA E-Sig Working Group Report \(WP V6\), February 24, 1992](#)

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more care and diligence in producing their IVU than have those IVU manufacturers that are not subject to FDA regulations and periodic site inspections.

If your IVU supplier is not a medical device manufacturer, we strongly recommend that you qualify your vendor through a site audit, especially their processes for cleaning, packaging, product testing, and product traceability.

Another compliance consideration is receiving IVU into your business. This needs to be different from receiving post style medical valves. It is recommended that IVUs be quarantined upon receipt, and inspected to verify conformance to order specifications. Once inspected and approved, they should be released from quarantine by your QC unit. If your units arrive pre-assembled with the cylinder, you should receive some form of acceptable documentation that confirms their qualification for medical service. This must be a documented activity. Medical gas firms also need to have a method for traceability for their IVU. Two reasons make this a requirement. First, should a manufacturer initiate a product recall,

you must have the capability to identify the affected units, either in inventory or as they return for re-filling. Secondly, CGA publication E-7, section 7.0 specifies that all medical flow meters shall be re-verified for proper flow at a minimum of every five years. Verification must be performed either by the manufacturer or by his authorized agent, and needs to be a documented activity. Some IVU manufacturers establish additional requirements for repair, maintenance, and calibration of their units. Users need to follow this guidance as well. Where appropriate, it is recommended that you incorporate the manufacturer's guidance into your SOP manual.

When filling IVUs, keep in mind that some of the early designs did not allow for an acceptable leak test of the unit in accordance with FDA requirements. Manufacturer's instructions typically specified a 24-hour hold time, as well as verification of the unit's gauge to ensure that no leakage occurred. If valves made to that early design are in your inventory, the recommendations the manufacturer of those valves need to be part of your SOP's.

The units need to be held in quarantine, and the release following the 24-hour hold needs to be approved by the QC unit.

The final point for discussion on IVU regards their apparent potential for damage in the field. It has been observed that a significant percentage of IVU return from customers damaged or in an altered state when compared to the typical cylinder / post valve package. While much of this damage is cosmetic, some types of damage can affect the unit's performance, especially when the damage affects vital areas of the IVU. Pre-fill inspection procedures need to specify a process for examining the units for damage, and your SOPs should specify what type of damage requires repair and re-calibration. Damaged IVU should be designated as out-of-service, segregated, and returned to the manufacturer, or his authorized agent, for repair and re-calibration. You should maintain records of this activity.

### *The Evolution of Micro Bulk Units*

The third technological change in medical gases is the evolution of micro bulk units into medical gas service. Initially, most firms focused their micro bulk units on industrial application deliveries. Today, firms are finding it can be cost effective to service small medical accounts with micro bulk, rather than with portable cryogenic liquid cylinders. From a patient safety perspective, a permanently installed system, filled from a small bulk vehicle, is potentially safer than relying on un-trained hospital workers to swap liquid cylinders, which has been the root cause in a number of patient fatalities over the last decade.

The first compliance requirement is to qualify your micro bulk units for medical service. Units that enter medical service, either as new or repaired units, or are transferred from industrial service, must be appropriately qualified to ensure that no residual contaminants reside in the vessel as it enters medical service. This qualification process applies to all micro bulk units in medical service, not just oxygen units. This qualification, or change-of-grade process, must be incorporated as part of your SOP's, appropriately documented,

and reviewed / approved by the QC unit. A second area of consideration is oxygen cleaning of vessels and components. It is recommended that all system components and service parts be appropriately cleaned for oxygen service, and applied to all medical gases, not just oxygen. Again, the reason is to ensure against any potential residual contamination.

Micro bulk units need to be fitted with product specific connections on the delivery hose and the customer storage units. A pipe thread or half-union type connection between the customer storage vessel and delivery unit hose is not acceptable. It is strongly recommend that bulk tank/hose fittings be used that conform to CGA product specific connection specifications for bulk units.

Another area of consideration is the filling of units on site. It is appropriate to fill ASME rated micro bulk customer tanks similar to other large stationary bulk tanks. This means that once filled, these

tanks do not have to be analyzed to USP specifications. Providing a certificate of analysis to the customer is sufficient. On the other hand, DOT specification portable cryogenic liquid cylinders, filled on-site from the micro bulk unit, need to be filled in accordance with all cGMP requirements that are applicable to filling the same type of unit at your facility. This includes label controls, pre-fill inspections, lot numbering, analysis of each unit to USP specs, and fill log documentation.

Transitioning to a new technology and ensuring FDA compliance does not have to be a painful process. A common key error is not thinking about compliance with governmental regulations until after a technological change is complete. Therefore, it is highly recommended that all firms incorporate a review of compliance issues as part of their project-planning phase. Reviews constitute a very useful tool; they can often identify requirements that, while the responsibility of the pur-

chaser, can to some degree be provided as part of the technology/systems vendor contract. For smaller firms this can be a major help in implementing compliant technology, but it assumes that these issues are identified and be part of the plan at the front end of the project.

GAWDA members have the GAWDA consultants to assist them during project planning. Manufacturers and producers of medical gases who are GAWDA members are encouraged to take advantage of this resource for guidance and assistance in ensuring that your next business technology upgrade meets established regulatory requirements.

**SGR**

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***For more information on FDA regulations and qualifying medical and specialty gas analytical instruments contact Ron Ball at B&R Compliance Associates LLC (317) 297-8518; e-mail: bob.yeoman@brcompliance.com, or visit B&R on the web at [www.brcompliance.com](http://www.brcompliance.com).***