How to avoid the top 10 FDA compliance citations

By following a few basic guidelines, medical gas distributors can achieve peace of mind relating to FDA requirements.

Every year the Food and Drug Administration (FDA) tabulates the top ten most common compliance citations. This information is drawn from all the inspectional observations made by its field inspectors during the year, and represents the output of over 1,000 domestic and nearly 300 international drug site inspections performed by the agency each year. While this data is drawn from the full spectrum of drug manufacturing, it should come as no surprise that the FDA's list of top deficiencies are also directly in line with the top compliance citations seen in the medical gas industry.

In 2007, FDA statistics show that the agency performed 1,250 domestic human drug manufacturing site inspections. That figure represents 40% of the 2,400 domestic registered sites. Internationally, the agency only inspected 296 – just 8% of the nearly 3,500 registered human drug manufacturing sites.

Here in the U.S., almost 64% of FDA inspections resulted in a clean bill of health for the firm. In 2007, less than 1% of domestic inspections resulted in the FDA taking official action in the form of a warning letter or seizure.

Internationally, the picture is a little different. Of the 296 international inspections in 2007, every one resulted in the firm having to implement some level of corrective actions, and 10% of the inspections resulting in FDA taking an official action such as issuing warning letters or worse.

Quality Control: the number one concern

The FDA's number one most commonly observed cGMP deficiency in 2007 involved quality unit responsibilities and procedures – *§21 CFR 211.22(d)*. Since the FDA considers the Quality Control (QC) unit to be the heart and soul that drives a good cGMP compliance program, it is not surprising that QC unit issues would top their list. QC unit deficiencies can take a number of forms, including the lack of independence of the QC unit from the operating group, the lack of adequate QC unit procedures, or the lack of involvement of QC unit personnel in decisions and approvals of critical processes and documents.

In the gases industry, citations involving the QC unit also are at the top of the list. A key reason for this is the small numbers of personnel at typical gas fill sites, and the resulting need to assign individuals overlapping quality and operational responsibilities. Whenever quality issues begin to take a back seat to production concerns, firms open themselves up to this type of violation. We frequently find that when companies start to cross this line, they fail to recognize the significant risk to which they have exposed their business.

Tribal knowledge is not enough

Two of the top five most commonly cited deficiencies in 2007 involve written procedures, or what most people refer to as the standard operating procedures (SOP) manual. It appears FDA finds many firms fail to have written procedures for production and process controls as required in §21 CFR 211.100(a).

In the gases industry this frequently takes two forms. In the first, firms simply do not have adequate written procedures, and simply rely on experienced personnel to ensure proper operation. We refer to this as the tribal knowledge method of producing medical gases. Under this scenario procedures on medical filling are passed down verbally from experienced people to new hires.

In the second instance, firms do have written procedures for most of their commonly performed tasks such as filling cylinders. However, they lack written procedures for issues that come up less frequently, such as customer complaints or performing a recall. A senior FDA inspector once confided to me that the agencies attitude is, if a procedure is not written, it is merely a rumor. Just because you might have an effective business process for dealing with an issue such as customer medical complaints, if the procedural steps for that business process are not written down in a procedure, which has been approved by your QC unit, your company is open to a citation.

> "In the FDA world your procedure manual is the bible, and describes how tasks are to be performed and documented."

This is a common situation in our industry, as many firms, in their desire to keep things simple, only put in their SOP manual those procedures they need to use on a daily basis. They fail to consider the full range of requirements they are subject to under 21 CFR.

In the SOP manual B&R offers to medical gas

companies, probably 30% of the procedures outlined are used infrequently by our customers – some almost never. We provide these procedures so that the firm can demonstrate full compliance of their written procedures manual to agency inspectors, and avoid this common FDA citation.

So shall it be written, so shall it be done

The next top five FDA observed deficiencies involve the lack of adherence to written production and process procedures. This usually involves two specific issues. Either firms are not adequately training and periodically re-training their personnel, or they have found their written procedures aren't exactly what is needed to get the job done, and therefore went ahead and made un-documented changes to work processes.

In the FDA world your procedure manual is the bible, and describes how tasks are to be performed and documented. There is nothing that says you cannot make changes to your work processes, but when you change them, you must also update your written procedures, and have them approved by the QC unit. If you fail to do this you leave yourself open to this type of citation under *§21 CFR 211.100(b)*. A common FDA inspection technique is to read your procedure, and then observe one of your employees doing the task to see if they follow the procedure exactly. To an FDA inspector, a firm that does not follow its written procedures makes it appear as if it is making things up as it goes along, even if the un-documented changes actually resulted in a better process.

Insufficient training

Employee training is also one of the top ten most common deficiencies. What many firms fail to realize is that the FDA expects everyone involved in the manufacture, distribution, testing, and release of medical gases to have annual cGMP refresher training. They also expect employees will receive periodic refresher training in standard operating procedures (SOP). The FDA does not stipulate how frequently this training needs to be performed, but every 2-3 years is a good guideline. The final issue where firms get cited on training issues is training of the QC unit. The FDA expects that periodically someone in the firm, usually the head of the QC unit for the firm, will receive documented training from an outside agency.

Laboratory controls are vital

The last most common compliance deficiency observed by the FDA involves laboratory controls – *§21 CFR 211.160(b)*. In our industry this frequently results from firms using analytical processes and equipment that have not been validated as equivalent to the USP/NF methods. Often correcting this type of violation is as easy as contacting the equipment manufacturer and obtaining a copy of the validation study they performed when the unit was brought onto the market. Another common issue in our industry related to laboratory controls is the failure to qualify the analyzer, and document that activity, once the analyzer has been installed at your facility, or when remote sample lines are added to the system.

Quick tips

I offer the following quick tips to help you steer clear of these common FDA violations.

Tip 1 – Make sure your SOP manual covers not only the basic requirements, but the full range of regulatory requirements your firm is subject to under FDA regulations.

Tip 2 – Make sure employee training is kept current, especially the annual cGMP refresher training.

Tip 3 – Perform a review of your processes, and watch your employees fill and test a batch of gas to make sure they are following your written procedures exactly. If they are not, either modify your procedures, or re-train your employees.

Tip 4 – If you have questions about any of this talk to a professional such as the experts at B&R for advice and direction on avoiding the most common FDA violations. SGR

Ron Ball

For more information on regulations that affect medical gas producers and end-users contact:
Ron Ball at B&R Compliance Associates LLC
+1 (317) 297-8518; e-mail: **ron.ball@brcompliance.com**; go to: **www.brcopliance.com**