



by Ron Ball

# Maintaining your cGMP Compliance Program in a Changing World

## FDA regulations that affect the medical gas industry change so rapidly that remaining in compliance is a daunting task, but can be done.

Since the year 2000, producers of specialty and medical gases have had to deal with many major changes in FDA requirements. The stream of small, incremental changes emanating from FDA and state agencies, as well as from within the medical gases industry itself, has flowed practically unabated. This article offers several recommendations that will help you set up and maintain an effective FDA compliance program that meets these demands head on.

A good FDA compliance program that meets these challenges can be compared to a finely tuned piece of equipment. And as with any piece of equipment you have come to depend on to ensure the smooth and trouble free operation of your business, your compliance program requires regular maintenance.

During audits, we frequently find that many companies fail to set aside the time and resources needed to review and update their programs—at least on an annual basis as required. Producers of medical gases often overlook recommendations such as those offered here, despite the fact that they offer a powerful tool that can smooth your compliance path.

### *Many Influences Affect You*

The need to upgrade your company's compliance program can be influenced

by a wide variety of conditions—both external and internal. The most obvious influence on your compliance program are the changes that proliferate in both 21 CFR and FDA guidance documents.

Specific changes in 21 CFR that affect medical gases are an infrequent occurrence, and are usually well publicized by both FDA and the industry associations, such as GAWDA and CGA. 21 CFR is the law of the land, and any changes to these regulations must be incorporated into a firm's compliance program no later than the effective date of the change.

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FDA guidance documents do not create a legal obligation on a manufacturing firm, but they do provide a clear indication of what FDA believes is acceptable compliance. Firms that choose not to follow specific recommendations in FDA industry guidance documents have the burden of demonstrating that their unique approach assures adequate compliance.

Over the years, our industry has worked closely with FDA on guidance documents, so they do incorporate many of the real world considerations from the medical gases industry. Following the requirements in these guidance documents demonstrates to FDA a degree of assurance that a firm's compliance program will pass muster during a site inspection.

Other external influences that affect your compliance program are state and federal medical facility site inspection and enforcement activities. Through their facility inspection program, regulatory enforcement agencies uncover issues that alter their thinking on what constitutes compliance. As enforcement agencies, they issue citations that prod firms to modify their compliance programs. This problem identification/citation process is another way in which the agency makes known that a change in their thinking has taken place on what constitutes compliance on a specific issue. By inspecting and citing many firms relative to the same issue, FDA has the ability to alter the definition of "current" good manufacturing practices in the industry.

This enforcement-based shift in agency thinking is not as well publicized as changes in regulations or guidance documents, and requires some detective work

to uncover. The good news is that the information is available—but you need to know where to look. FDA maintains a database of warning letters that can be searched by subject and by company to assist firms in keeping abreast of recent enforcement activities. As GAWDA’s FDA consultants, B&R monitors this information to track developing enforcement trends in our industry.

A number of other internal processes can influence a firm to update its compliance program. These include:

- The adoption of a new technology for filling or delivering medical gases
- Acquiring and integrating a new business or production site into your operation.
- Changes in QC Unit personnel that may necessitate an update of your compliance program.

It is thus desirable that procedures outlined in your standard operating procedures (SOP) manual be reviewed periodically. This is a key element in ensuring that your compliance program remains current with evolving regulations and developing enforcement trends.

Your compliance program is one of the very first areas an FDA inspector will review during a site inspection. Your SOP manual needs to provide detailed guidance on the many different activities involved in your medical gas filling operations. Generic manuals, or those that refer to the requirements in other publications, and which do not provide a step-by-step guide to performing a task, may not be adequate. For example, we often see SOP manuals that simply refer the reader to CGA documents that cover high-pressure, pre-fill inspections and do not establish the step-by-step pre-fill requirements published in the manual. This would be acceptable, however, only if a current copy of the referenced CGA publication was part of each SOP manual your firm uses. It is also important to ensure that your manual covers all of the required topics for cylinder inspection and fill processes, as well as QC Unit operations.

Your SOP manual should also include

procedures for:

- Label controls
- Incoming materials inspection and release
- Product analytical processes
- QC Unit procedures for product release,
- Lot number formulation
- Product distribution and tracking
- Recalls
- Methods for conducting investigations of non-conforming products and materials
- Customer complaints.

One way to make this SOP manual review process more manageable is to divide the contents of your SOP manual into twelve units, and require monthly reviews of one of the units. Don’t forget to review any forms associated with the procedures under review. Any changes to procedures or forms will require that you conduct update training with your employees, and that the training is documented.

Additional procedures and processes that should be included in your cGMP maintenance program include the requirement that all corrective actions are

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verified, fully documented, and closed appropriately.

Increasingly, we see the FDA scrutinizing more closely firms that find and fix their own compliance problems and do not wait for an FDA inspector to come and inspect. Corrective actions that can be conducted internally may include:

- Conducting an internal audit
- Receiving a customer complaint
- Performing a non-conforming product or component investigation.

Corrective actions can also result from an external agency inspection.

## ***Service Issue or Violation?***

It is important to identify why a particular issue occurred, and to develop and implement a system-wide corrective action to prevent that issue from recurring. A common example we often see, and which helps to illustrate this point, involves customer complaints. It is not uncommon for medical gas firms to find out from a customer that a cylinder is empty. Many firms do not treat this as a customer complaint, but view it as a customer service issue; i.e., they simply give the customer a new cylinder or a credit.

In reality, these are medical complaints, subject to the requirements in 21 CFR. These complaints need to be collected, and each incident investigated to determine the root cause of the incident. Any causes of the incident need to be identified, and corrective actions initiated and completed. All this activity must be documented. Too often, we observe companies with complaints that have never been adequately documented, or have never been closed and remain open long after the complaint was recorded. Thirty to sixty days is the typical standard in the industry for closing a medical complaint. A component that should be included in every cGMP maintenance program is the requirement to conduct a monthly review of all open complaints to determine status. Also, it should require that all medical gas credits be reviewed to determine if they were, or should have been, recorded as a complaint.

## ***Mock Recalls Pinpoint Weaknesses***

Mock recalls represent another maintenance program item we strongly recommend. This process involves selecting a group of lot numbers and implementing your recall procedures. This process lets you determine the status of each container of medical gas. A status report could include the amount of product in inventory at a customer’s central location, or at a branch where a shipment may be scheduled for delivery to a customer.

Traditional wisdom in the pharmaceutical industry holds that a “mock recall”

can identify between 90-95 percent of all products subject to recall. However, in the pharmaceutical industry it is not uncommon for a lot of drugs to contain thousands of containers that must be recalled.

Since our industry is involved with much smaller lot sizes, we recommend that you strive to achieve a recall effectiveness of 100 percent. If you run 6-10 lots and can not reliably achieve the 90-95 percent recall level in each of them, we recommend that you take a very hard look at your recall procedures or at your lot number tracking systems to identify potential improvements. This relatively straightforward, table-top exercise is simple to conduct and it helps ensure that, in the event of an actual product withdrawal or recall, your systems work properly. Also, that it can be relied upon to accomplish the task quickly and effectively, and confirms that your compliance and operations personnel are familiar with how to conduct a recall.

### *Employee Training is Paramount*

Employee training is yet another area that is commonly overlooked by medical gas firms. Not only are you required to ensure that employees are fully trained before they begin to perform medical gas manufacturing activities, you also have the responsibility to provide periodic update and refresher training. FDA strongly recommends that all employees receive, at a minimum, annual cGMP refresher training. This includes not only fillers and pumpers, but drivers and warehouse personnel as well. This requirement also covers branch operation employees, where medical gases are only distributed and not filled. If you make changes to your SOP manual procedures, or to your forms, all affected employees must receive update training, and this training must be documented. An additional requirement is professional training for your QC Unit personnel. If your firm maintains its own compliance program, the individuals affected should receive annual training, and also participate in other available training venues, such as the GAWDA teleconferences, to stay abreast of on-going regu-

latory developments. FDA understands that a direct link exists between properly trained employees and a strong cGMP program, and that firms without properly maintained employee training documentation run the risk of receiving a citation during their next site inspection.

### *Requirements Proliferate*

Many additional basic elements can be part of an adequate cGMP maintenance program. While we find that firms are typically more aware of these, they are still worth mentioning. Basics requirements include instrument and analytical equipment calibration and maintenance—analyzers, scales, flow meters, pressure transducers, thermometers and pressure gauges, or any other test equipment that must be periodically calibrated. In some instances it may be necessary to return an analyzer to the manufacturer for calibration and/or maintenance.

Maintenance of documentation also falls under the “basics” category. It includes:

- Reviews of completed documents to find and fix appropriately any incomplete or missing data or signatures in your cGMP documentation.
- Making appropriate document corrections in accordance with cGMP requirements.
- Purging files of documents no longer required to be retained.
- A cGMP maintenance program is just as important to the long-term health of your business as the maintenance programs used to ensure the proper and efficient operation of equipment and vehicles. Documentation reviews should include:
  - An annual review of any equipment, computer, or process validations your firm may have performed to determine if the validated conditions still apply.
  - Changes made to the system or process, or maintenance activities that may have created a need to perform a partial re-validation.

- Assurance that all of your state and FDA licenses are up to date, and that you are registered in every state to which you ship/sell medical gases.
- Finally, some basic equipment items may have been overlooked. We recommend that these be included in your cGMP maintenance program:
  - Many flexible pigtails come with expiration dates printed on the information tag attached to the pigtail. These items should not be used beyond their expiration date. We recommend that all pigtails be inspected annually to verify that they are not expired.
  - Vacuum pump oil is another item which often gets overlooked. Your vacuum pump oil should be checked periodically, based on usage, and the oil changed as necessary to minimize wear on the pump. This also ensures full operation of the vacuum system.

When properly maintained and updated, your FDA compliance program can help prevent your business from being negatively affected during a future FDA or state agency inspection. This prevents your having to spend valuable time and resources to correct citations or inspectional observations. cGMP maintenance is really a case of “pay me a little now, or pay me much more later.”

Firms that institute proactive cGMP maintenance programs are generally viewed by FDA as lower risk firms, and may find that they are subjected to fewer site inspections over time. While there is a cost to preventive compliance program maintenance, the long term potential cost savings outweigh the short term maintenance costs by a large margin. **SGR**

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