

Standard Operating Procedures

Overview

All companies who fill medical grade gases must develop written Standard Operating Procedures covering those operations subject to Current Good Manufacturing Practices. The procedures must be sufficient in detail to enable employees to perform required job duties. Therefore, SOPs should present a systematic approach to medical gas operations.

Principal Violations of SOP Requirement

The principal violations noted during FDA inspections which pertain to written operating procedures are:

- Failure to follow SOPs — Companies perform operations differently than specified in the SOPs or fail to perform functions required by the SOPs.
- Using another company's SOPs — Similar to the above, a company's SOPs simply do not fit the operation. (Note: there is no violation, *per se*, in adapting another company's SOPs to your operation, provided they are amended to fit what you do).
- Insufficient detail in SOPs — Companies' SOPs lack sufficient detail to explain a procedure or worse, omit necessary procedures entirely.
- Failure to "approve" SOPs — Quality Control fails to date and approve SOPs prior to putting them into use.

Scope

The following guidelines represent principal operational areas which should be addressed in written SOPs. They may not represent every item identified in Title 21 CFR for which written procedures are required nor every item which the FDA may wish to be addressed. In addition, any company rules or "ways of doing things" relative to medical gases are, in fact, operating procedures and should be included in your SOPs.

Principal SOP Elements

Every company's SOPs will likely differ in form, content, and detail.

- Format. The format used is entirely up to you. You may have chapter headings, page headings, etc – whatever you like.
- Detail. The degree of detail required is unclear. Explain the procedure or company rule in a manner which you think is clear and concise. You may want to ask a new employee, or an employee not involved with medical gases, to proofread your draft for clarity. His/her understanding of the various procedures will give you a good idea as to the sufficiency of detail necessary.
- Content. 21 CFR, §211 states specific areas which must be covered in SOPs. Methods which are acceptable to the FDA for meeting many of these requirements are covered in the *Compressed Medical Gases Guidelines* (see TAB 5). The following list is not intended to be all-inclusive but represents most major medical gas operations which should be covered in your SOPs:
- Quality Control Unit
 - Training
 - Periodic self-audit
 - Equipment
 - Drug gas components
 - Drug gas containers and valves
 - Labeling
 - Drug gas testing
 - Lot numbering
 - Batch production and control records
 - Product Specifications
 - Laboratory records
 - Holding product (quarantine and storage)
 - Distribution
 - Complaints
 - Recalls
 - Investigations

Quality Control

Every manufacturer must have a Quality Control Unit to oversee medical gas operations. The Code does not stipulate the number of members required or limited to serve on the QC unit but does require training, education and/or experience necessary to perform their job duties.

Duties of the QCU are varied. Required duties include: approval (with authority to reject) drug product, containers, labeling, production records, procedures and specifications. If recordkeeping errors or deviations from the SOP has occurred, the QCU should investigate. To carry out these duties effectively, the QCU also typically oversees training, performs routine self-audits, and responds to complaints.

SOP – The SOP should identify QCU members by name or title and define their responsibilities.

Training

Each employee and supervisor must have education, training, and experience, or any combination thereof, to enable that person to perform assigned functions.

Training must be in the particular operations performed by the employee (including functions covered by SOPs and cGMPs), ongoing with sufficient frequency to ensure that employees remain familiar with their assigned job duties.

Trainers must also be qualified (by reason of education, training, and experience, or any combination thereof).

SOP – The SOP should describe your training program: identify trainers, frequency of required training, and describe the type of training which will be given (i.e., “classroom, OJT, practical demonstration, etc”).

Self-audits

Self-audits are important for finding and correcting problems before the FDA finds them and, more importantly, before a catastrophic problem occurs involving a patient.

A self-audit should be performed by one or more members of the Quality Control Unit at least annually (more frequently, if circumstances warrant). The use of “outside” auditors (i.e., consultants) or QC members from other branch operations may be helpful but is not required by the FDA.

The audit should be designed to assure conformance with your SOPs and identify provisions of your SOPs which need expanding. Audits also uncover areas in which particular employees need additional training. You may want to print a draft copy of your SOPs to use (markup) in auditing as you will likely note sections which should be improved.

SOP – The SOP should identify who will perform self-audits (by name or job title), how often self-audits must be performed, what is to be audited (you may simply refer to a checklist or name specific areas of operation), who is responsible for any needed corrective action, and followup.

Equipment

You should establish rules and specifications for determining that equipment is suited for the job and properly maintained. An important aspect of this is procedures designed to assure that the proper gas is put into the proper containers. For example, procedures should consider use and control of adaptors, assurance that indexing pins are in place in “yoke” style fittings, assurance that the proper type oil is used in vacuum pumps, etc.

The Code requires equipment used in medical gas production to be “routinely calibrated, inspected, or checked according to a written program designed to assure proper performance” and appropriate records maintained (§211.68). These procedures should be described in your SOPs.

SOP – The SOP should identify equipment used in the plant and specify the type of inspections/maintenance required, frequency of inspections/maintenance and an explanation of how to perform the procedure. An important aspect of inspections and maintenance is cleanliness. Your SOP should state what is to be done with equipment that requires cleaning.

If you want to use outside sources for such equipment as gauges and scales, say so. Be sure to state that appropriate documentation must be received and maintained on file. You may also want to specify a vendor by name.

Suggestion – You may also wish to specify preferred vendors and model/part numbers for equipment or other items used in medical gas production (leak check solution, cylinder valves, etc).

Drug Gas Components

When you receive a delivery into your bulk tank, the new product mingles with the existing product to produce a separate batch, which may be of different purity than the product prior to the delivery. The product in your bulk tank is a “drug gas component” (for pure gases, it is 100% of the finished product) which must be analyzed prior to filling cylinders.

If the first cylinder filled after a bulk delivery has been made is a single-component, noncryogenic gas (e.g., compressed oxygen), you may perform component testing and finished-product testing together by analyzing a cylinder filled from the first manifold. However, if the first cylinder filled after a bulk delivery is a mixture or is a cryogenic, you must first test the bulk container directly or a high-pressure, single-component cylinder filled after receiving a delivery. The reason for this is that, unlike cryogenic cylinders, high pressure cylinders are evacuated prior to filling so you may be assured that the filled gas is representative of the bulk.

SOP – The SOP should state your company’s policy regarding frequency of component testing (immediately after each bulk delivery) and method of testing (direct bulk testing, first high-pressure, single-component cylinder).

Drug Gas Containers and Valves

Your SOP should provide an explanation of how to perform each necessary prefill inspection for any container you fill with medical gas (high-pressure cylinder, cryogenic dewar, bulk container).

SOP – The SOP should list prefill steps with a description of how to perform each. Rather than explain each prefill step, you may choose to reference another document, such as CGA Publication P-15 or a vendor’s plant manual, thereby incorporating them into your SOPs. If you do so, you may wish to specify exactly which paragraphs or sections you are incorporating to avoid being held to the entire standard or manual.

Labeling

The FDA requires strict physical control over labels and procedures to ensure that labels are current and conform to specification. Typically, Batch Production Records note labels issued, used, destroyed/returned and distributors use a separate log (e.g., “Master Label Log”) for recording total labels in inventory.

SOP – Your written procedures should cover receipt, storage, issuance, return of unused labels, labels destroyed, and when to apply and remove labels to/from cylinders. SOPs should also state when labels are to be issued and where maintained (e.g., state specific secured location).
Note: Be sure to include sample labels in your SOPs.

**Drug Gas Testing (211.165) and
Laboratory Records (211.194)**

Finished drug products must be tested. You are required to have written procedures which describe methods of sampling and the number of cylinders per batch to be tested. To do so, your SOP will need to define “batch” for each type of gas you fill (single-component gas filled via manifolds, liquefied gases, cryogenic gases, bulk). At a minimum, the FDA considers a batch (or lot) to be an uninterrupted filling cycle using the same personnel and equipment. e.g.,

In addition, your SOP must state how samples will be tested. Be specific. If you reference a particular type of analyzer, refer to equipment by type and part number or item number (if you number your equipment). Include directions for calibrating and operating the equipment (you may refer to the manufacturer’s operating instructions, thus incorporating them by reference, rather than rewriting the operating manual). i.e., “The xyz analyzer, (analyzer #5) shall be used to analyze Oxygen, USP, and shall be zeroed, calibrated, and operated according to the xyz operating manual.” You must also include provisions for remedial action in the event accuracy and/or precision limits are not met.

SOP – Your written procedures should identify what is considered to be a “batch” (or lot) and specify how many samples/batch will be tested, how they will be tested, and what will be done in the event specifications or testing accuracy cannot be met.

SOP – The SOP should explain what equipment will be used to test what gases, how the equipment is to be calibrated and how often, and how calibration and testing records are to be kept.

Lot Numbering

You must provide for a means of identifying cylinders to their respective fill records and source (bulk) fill records. Your lot numbering scheme is up to you but most companies use a code representing:

- Location (if filling at multiple facilities)
- Manifold designation (if more than one manifold is in the plant)
- Date (Julian dates are commonly used)
- Specific lot

SOP – Create a lot numbering scheme. For clarity and training purposes, it is best to include a sample lot number with an explanation of the meaning of each digit/letter.

Batch Production & Control Records

Filling records are typically joined with cylinder prefill inspection records, postfill records, and label issuance records on a Batch Production Record (i.e., Pumper's Log).

- Prefill. See *Drug Gas Containers and Valves* (p.5).
- Fill. As with other aspects of your SOPs, you may reference another document, such as a vendor's plant manual or industry standard, instead of writing out each detail of the filling process. For single-component nonliquefied gases, this process usually consists of "heat of compression" check, filling according to a pressure/temperature correlation chart, heat-of-compression check, and leak check while filling.
- Postfill. Cylinders should undergo a final leak check before being analyzed (see *Laboratory Records*).

SOP – The SOP should explain how individual gases are to be filled and the steps taken during the prefill, fill and postfill process. If you incorporate other documents by reference, you may wish to limit certain paragraphs or sections of the other document(s) unless you wish the entire incorporated document to become part of your SOPs.

Product Specifications

What standards do you set for your medical gases? Obviously, laboratory technicians must know whether a finished product (or stage of production, if applicable) is acceptable or unacceptable. The USP (United States Pharmacopeia) has published monographs of acceptability limits. In addition to a stated minimum assay, maximum impurities are often specified (see TAB 8). However, companies often establish product specifications which are more stringent. When you specify product specifications, be mindful of three things:

1. You will be held to the standards you set, if they differ from the USP.
2. Your specifications should be equal to, or 'better', than the USP.
3. The absence of a stated impurity does not relieve you from ensuring that no harmful contaminants are present.

Holding Product

Procedures must describe warehousing of medical gases. Two warehousing issues which must be addressed are: quarantine of medical gas cylinders prior to release for distribution (by the QCU) and rotating stock so that the oldest batch(es) are distributed first.

SOP – Explain when product is to be quarantined from other product and where. When will the product be released from quarantine and where will it be put? Also, what procedure will be employed to ensure that the oldest product will be distributed first?

Distribution

When drug gases are distributed, some means of tracking must be provided to ensure that a recall, if necessary, can be carried out. Although lot numbering is the most common method of identifying cylinders to their respective Batch Production Records and Bulk Delivery Records, transponders and bar coding are also effectively used in the industry.

SOP – The SOP should explain your procedure for ensuring that a recall can be effectively carried out.

Complaints

Complaints, whether oral or in writing, must be investigated and brought to a conclusion. A compliant file must be maintained (even if no complaints have been registered) which must contain the following information regarding any complaint:

- Name and purity of the drug product;
- Lot number;
- Name of complainant;
- Nature of complaint; and
- Reply to complainant.

SOP – You must have written procedures describing the handling of all written and oral complaints, including complaints regarding cylinders, valves, labels, etc.

Investigations

Investigations should be conducted when Operating Procedures aren't followed, when complaints are received, when equipment fails to perform as required or product fails to meet specifications, etc. In other words, whenever any part of your medical gas program fails to perform as intended, you should find out why, either justify the deviation or make an appropriate corrective response, and document your actions.

SOP – Your SOP should explain the type of events which would necessitate an investigation, who (or list by title) is responsible for investigating events, and require followup to ensure that the event has been resolved completely.

Recalls

The possibility that a product recall may be necessary is something we don't like to think about, but it is something we must plan for. Strangely enough, Murphy's Law seems to apply more often than not – the graver the decision, the more likely the boss will be on vacation.

Your written procedures should explain the type of events which would necessitate a recall (e.g., discovery that a sample has failed to meet specifications after distribution, discovery of a potentially harmful contaminant in a sample after distribution, etc.), who (or list by title) is responsible to effect a recall, how products subject to the recall will be determined, how specific customers who received the lot will be contacted, and time frames for accomplishing a recall.

SOP – Your SOP should explain the type of events which would necessitate a recall and the procedure to ensure that a recall can be effectively carried out.

Other

Many cGMPs contained in Title 12, CFR §211.44 were not written with compressed gases in mind. Therefore, it is not surprising that some regulations do not seem to fit our industry. Nevertheless, some FDA inspectors have attempted to enforce requirements for written procedures for such things. §210.2 specifically requires compliance only with those regulations applicable to the operations in which you are engaged. 21 CFR, §210 and 211 (cGMPs) may be found behind TAB 10 of this manual.

ADMINISTRATIVE		Section: 1	Page 1 of 2
MEDICAL GAS PROCEDURE	Approved:	Date:	
<p>11.01 EQUIPMENT CALIBRATION</p> <p>1. Calibration records shall be maintained in the Plant Manager's office. These records shall be kept with other appropriate production records, and readily available for inspection by management or any appropriate government representative.</p> <p>11.02 High pressure gauge(s)</p> <p>1. Pressure gauges shall be calibrated <i>annually</i>, or more frequently if recommended by the manufacturer, according to the manufacturer's instructions by a company who regularly performs gauge calibrations. If the manufacturer specifies a particular method of calibration, that method shall be communicated to the company performing calibration. Otherwise, the company performing calibrations shall be instructed to calibrate to NIST traceable standards.</p> <p>11.03 Scales</p> <p>1. Scales shall be calibrated <i>annually</i> according to the manufacturer's instructions by a company who regularly performs scale calibrations and is licensed by the State or county. If the manufacturer specifies a particular method of calibration, that method shall be communicated to the company performing calibration.</p> <p>11.04 Vacuum Gauge(s)</p> <p>1. Vacuum gauge(s) shall be calibrated <i>annually</i>, or more frequently if recommended by the manufacturer, according to the manufacturer's instructions by a company who regularly performs gauge calibrations. If the manufacturer specifies a particular method of calibration, that method shall be communicated to the company performing calibration. Otherwise, the company performing calibrations shall be instructed to calibrate to NIST traceable standards.</p> <p>2. Vacuum gauge(s) shall be visually inspected daily, prior to use, to ensure that the indicating needle rests on "zero" with no pressure or vacuum applied. A notation of this inspection must be made on the Batch Production Record.</p>			

CYLINDER LABELING		Section: 10	Page 1 of 4
MEDICAL GAS PROCEDURE	Approved:	Date:	
<p>10.01 Master label file</p> <p>1. A current label sample will be maintained in a "Master Label File" and in this manual (see 10.05, 10.06 and 10.07).</p> <p>10.02 New labels</p> <p>1. Modifications to labels shall have a date revision code. This code shall be used to assure that the most current labels are being used.</p> <p>2. When new or additional labels are received, they will be checked for accuracy by a QC team member by comparing with the approved proof label and a verified count will be made, updating the master label log as appropriate.</p> <p>10.03 Label storage</p> <p>1. USP/ NF labels will be stored in the cabinet marked "LABELS" located in the Plant Manager's office. Access will be limited to the Plant Manager and anyone specifically designated by him.</p> <p>2. Industrial product labels will be stored separately from medical gas but may be in the same room, as designated by the Plant Manager.</p> <p>10.04 Daily Label reconciliation</p> <p>1. Label issuance must be reconciled with the number of cylinders actually relabeled. Labels issued, used (applied to cylinders), destroyed, and returned to inventory shall be noted on the Batch Production Record.</p>			

Note: The above sample SOP pages have not been approved by the FDA, but is intended to serve as an example of how an SOP may be organized.

Recordkeeping

Overview

The FDA does not mandate any specific format for forms, although certain information must be recorded. You may combine required information to consolidate your paperwork, if you desire. For example, a typical Batch Production Record would be used to record prefill, fill, and postfill activities. However, many companies also list daily label reconciliations, equipment data, and daily vacuum gauge checks on their production records.

Master Label Log

This log is used to keep a running inventory of each gas' label. Typically, the log lists:

- date
- beginning balance
- labels issued
- labels returned
- labels added (new labels received from vendor)
- labels destroyed (obsolete labels removed from inventory)
- ending balance
- signature or initials
- reviewer

Equipment Maintenance Log

This log is used to record cleaning, maintenance and use on major equipment associated with any activity which would affect the purity of the gas, cylinder or valve (except routing maintenance such as lubrication and adjustments). Therefore, activities such as replacement of pigtails, manifold valve replacement or repair, etc. would be recorded. (Note: Make sure you have complete training records of any personnel performing maintenance activities. Training is required by FDA, OSHA, and in many cases, DOT). Hydrostatic retest records may be referenced for most cylinder maintenance.

Calibration Logs

Although Calibration logs may be combined with Equipment Maintenance Logs, it is probably best not to do so, since Equipment Maintenance Logs encompass much more than just equipment requiring periodic calibration.

Calibration logs are used for recording “calibrations, inspections, and checks” as required by §211.68. Typically, a separate log will be created for each high pressure gauge, vacuum gauge, thermometer, scale, and each analytical instrument, although you may find it easier to record some of these – especially activities performed daily – directly on the Batch Production Record.

In lieu of maintaining a multitude of logs, you may simply file the calibration reports for each piece of equipment calibrated by an outside company. This is a bit risky, however, because it is easier to overlook due dates.

Time intervals for calibrations are determined by equipment manufacturers’ recommendations. In the absence of such recommendations, the FDA requires equipment to be “routinely” calibrated with a frequency to “assure proper performance.” Historical data from past calibrations can be used to determine appropriate calibration schedules. If the manufacturer has no recommendations and you have no historical data, consider annual calibration for gauges, semiannual calibration for scales, monthly calibration for thermometers, and weekly calibration for electronic instruments. You should alter these schedules when historical data is available which indicates a more appropriate schedule.

A typical gauge calibration log would include:

- Gauge number (or serial number, as reported on the calibration report)
- Date last calibrated
- Recalibration due date
- Signature or initials
- Reviewer
- Use or location (optional)

If you calibrate your own gauges, you would also need to include specific calibration and traceability data.

Thermometers should be calibrated according to the manufacturers' recommendations. Electronic, mercury filled, and the more common magnetic, spring loaded thermometers are all within use in our industry and, of course, your procedure will differ among these. When the manufacturer has made calibration recommendations, your SOP would incorporate these procedures and your log should show calibration at the recommended intervals. In the absence of manufacturers' recommendations, the FDA has stated that they will allow a visual comparison with a similar thermometer which is not used in production. The allowable difference between the two is determined by the increments stated in your pressure/temperature filling charts.

Electronic instrumentation, such as a paramagnetic analyzer, should be calibrated according to the manufacturers' recommendations. (Often, attaining a "zero" baseline is required prior to calibration, which should also be recorded in your log, as this is an essential step in achieving proper readings). The information recorded in your log will differ depending upon the particular equipment and what is required to calibrate but it is important to record enough information to show that calibration (and "zero," if required) was performed, by whom and when, and reviewed. Since calibrations are only as valid as the standard(s) used, if calibration and/or "zero" gases are necessary, your log should also identify the gas standard(s) used by reference to cylinder serial number (or certificate of analysis).

Wet chemistry analytical methods require periodic changing of chemicals. To ensure that the readings obtained are still valid, you would need to periodically "calibrate" the method by comparing a reading against a known standard gas.

Scales are usually calibrated by professional scale maintenance companies. A calibration log is useful to avoid forgetting recalibration due dates but be sure to maintain your calibration reports on file.

Detector tubes do not require calibration but do have expiration dates. You should record this check either on a calibration log or directly on your Batch Production Record.

Batch Production Record

The Batch Production Record (BPR), sometimes called a "Pumper's Log," is the document in which you record cylinder prefill, fill, and postfill activities. As stated earlier, you may consolidate recordkeeping information by recording additional data which must be also be maintained, such as daily label issuance and calibration and equipment inspections. At a minimum, it is suggested that your BPR include the following for high pressure cylinders:

- Product identification
- Identification of filler, date, and reviewer
- Lot numbers
- Identification of cylinder types/sizes
- Identification of equipment used (i.e., manifold designation)
- Cylinder Prefill Inspections
 - Color
 - DOT marking (retest date, ownership, pressure rating, cylinder specification)
 - Label
 - Visual
 - Valve inspection
 - Odor test (if applicable)
 - Hammer test (if applicable)
 - Vent
 - Evacuate
- Fill Procedures
 - Heat of compression
 - Pressure (record the actual pressure)
 - Temperature (record the actual temperature)
 - Leak check
- Postfill Procedures
 - Leak check
 - Odor
 - ID
 - Purity (record the actual purity)

At a minimum, it is suggested that your BPR include the following for cryogenic (DOT 4L) cylinders:

- Product identification
- Identification of filler, date, and reviewer
- Lot numbers
- Identification of cylinder types/sizes
- Identification of equipment used (if multiple fill stations)
- Cylinder Prefill Inspections
 - Visual
 - DOT marking (specification)
 - Label
 - Contents gauge

- Pressure relief device (condition and pressure setting to determine fill density)
- Odor test (vapor phase only, if applicable)
- Valves
- Purge
- Fill Procedures
 - Tricock (if applicable)
 - Weight (if applicable)
- Postfill Procedures
 - Odor test (vapor phase only, if applicable)
 - ID
 - Purity (record the actual purity)

Complaint Log

Create a compliant form to show, at a minimum:

- Name and purity of drug product
- Lot number
- Name of complainant
- Nature of complaint
- Reply to complainant
- Investigation and followup
- Reason investigation was not conducted
- Signature, reviewer, date

Bulk Deliveries (receipt of bulk product)

Bulk delivery receipts with a Certificate of Analysis should be maintained. There are several ways of doing this: you may file all bulk delivery records together or simply keep a log showing delivery dates and attach delivery records to Batch Production Records, etc. The two important aspects of maintaining these records are (a) to be able to trace product back to its source and (b) to be able to show that no liquid product was filled prior to bulk testing.