Validation of Process Gas Systems

By Jeff Hargroves

Validation of process gas systems involve documenting the expected system behavior, and verifying that the system performs as expected. This article covers the pertinent aspects of IQ, OQ, and PQ related to process gas systems and many of the potential problem areas. The validation of nitrogen and compressed air systems, including breathing air systems, is used as an example which can be extended to the validation of most other process gas systems.

Why Validate Process Gases?

Process gas systems may include compressed air, nitrogen, oxygen, helium, or other inert gases. If the gas is used to operate product related system(s), or directly affects the manufacture of drug products, we must demonstrate the system can continuously operate in a state of control.

Inspection agencies require that we demonstrate control over utilities that can potentially impact a product. However, the methods we use to document and demonstrate control of utilities are currently a source of debate in the field of validation. For example,

- Will contractor start-up documents suffice?
- Is commissioning, using “Good Engineering Practices” adequate?
- Are traditional, preapproved validation protocols necessary?

There is no pat answer. Generally, we must demonstrate that the process gas delivered at the point-of-use meets the predetermined user requirements. As long as we demonstrate this, it does not matter what we call the demonstration documents.

Design Considerations

As with any other cGMP system or equipment, we must design nitrogen and compressed air systems so that they can be qualified. The design process begins and ends with documentation of the point-of-use requirements for the system.

A typical compressed air system consists of the air compressor(s), driers (desiccant or refrigerated), distribution piping, and filtration systems. A typical nitrogen system consists of either a liquid nitrogen storage tank and vaporizer or nitrogen bottles, distribution piping and filtration systems.

Breathing air systems are becoming more commonplace as our industry increases the research and production of potent and toxic drugs. The qualification of breathing air systems is generally similar to that of other process gases. However, there are some specific, generally accepted requirements.
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Figure 1
Minimum Requirements of a Compressed Air or Nitrogen System

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical Acceptance Criteria</th>
<th>When to be concerned about this characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure, min. &amp; max.</td>
<td>90-110 psig</td>
<td>Usually to meet equipment needs; max. is important if equipment is not capable of throttling pressure.</td>
</tr>
<tr>
<td>Flow, min.</td>
<td>≥ 10 scfm</td>
<td>Usually to meet equipment needs; max. is important if equipment is not capable of throttling flow.</td>
</tr>
<tr>
<td>Temperature, max.</td>
<td>≤ 90ºF</td>
<td>Seldom important, except for breathing air, unless there is a specific process requirement.</td>
</tr>
<tr>
<td>Purity</td>
<td>Meets USP Monograph</td>
<td>Use only if required.</td>
</tr>
<tr>
<td>Particulate</td>
<td>Meets particulate class level as defined by Federal Std. 209E</td>
<td>Same requirement as the room in which the gas is introduced, tighter if product contact issues dictate.</td>
</tr>
<tr>
<td>Microbial</td>
<td>Meets microbial limits, as defined by your company, for given room classifications</td>
<td>Same requirement as the room in which the gas is introduced, tighter if product contact issues dictate.</td>
</tr>
<tr>
<td>Dewpoint</td>
<td>≤ -40ºF</td>
<td>Process driven. (Don’t claim -40ºF if your process doesn’t need it).</td>
</tr>
<tr>
<td>Hydrocarbon</td>
<td>Non-detectable, (eg ≤ 25ppm as measured with Draeger 10a/P hydrocarbon tubes)</td>
<td>Process driven, generally “non-detectable” for process applications. Specify the lower “non-detectable” limit.</td>
</tr>
</tbody>
</table>

for breathing air systems.

Figure 1 lists the minimum requirements that should be considered during design of a compressed air or nitrogen system.

Process Gas Standards

Currently, there are no universally recognized standards for the validation of process gases. However, a group within ASTM subcommittee 48.06 is developing validation standards for the process gases, and for the methods used to test the gases. There are several places to go for direction on the requirements of process gas systems. Generally, process gas systems must meet the chemical, microbial, and purity requirements of the products they will potentially contact, and the requirements of the room into which they are exhausted, if applicable.

The USP has developed test monographs for process gases, such as medical air, nitrogen-99%, nitrogen-75%, and oxygen. Care should be taken to consider the particular process application before assuming that conformance to USP specifications is required. Some of these methods are difficult to execute in the field (e.g., Nitrogen-99%), and should not be attempted unless they are required.

For microbial and particulate monitoring, the specific criteria developed in our respective facilities for class 100,000, 10,000, 100 and so on, should be consulted. In general, the process gas must not negatively impact the room into which it is exhausted.

For breathing air systems, the NFPA 99 specifications for breathing air is used as the basis for acceptance criteria. Additional guidance can be found in the journals of the Compressed Gas Association.

Use of Final Filters

The use of the air should always be considered when deciding what type of filter, if any, is required. Compressed air and nitrogen are often used to power...
equipment and motors in the process areas. In classified (such as 100,000, 10,000, and 100) areas, where process gases directly contact the product, final filters are advisable.

Point-of-use filters should be in place, or at least considered during PQ of the system. Many companies qualify the system without the point-of-use filters in place to ensure system integrity even if the filter develops a leak during its use.

Filter model numbers should be documented, and controls should be established to ensure the same filters are used over the life of the system. The manufacturer may vary, but critical characteristics, such as filter materials, flow rate, and particulate filtration levels must be maintained. This information can be documented in the system or equipment SOPs, or in the maintenance management system. The filters found in the system two years after the initial qualification must have the same critical characteristics as the filters that were originally designed, specified, and qualified.

Final filters serving class 100, or cleaner areas, should be integrity tested. The frequency of testing should be commensurate with their use. For this reason, it is often advisable to locate the filters outside the process area. A common design approach is using medical grade copper in the distribution system, transitioning to stainless before entering into process areas, with dielectric couplings at the transition. This transition point is usually a good place to locate the system’s final filters.

Installation Qualification Issues

As with any cGMP system or equipment, every inch of the system should be checked to verify conformance with as-built drawings, construction materials, valves, cross-connection to other systems, and unused portions of the system. In any large, unused portion of the system, adequate protection preventing fluid buildup during system shutdown, which could compromise the microbial purity of other parts of the system, must be ensured.

All alarms must be tested, including those on the compressors and desiccant driers for the compressed air system, on the storage tanks and vaporizer for nitrogen systems, as well as on the distribution system itself. It is often useful to hire the service representative to conduct these tests. These experienced personnel can test the alarms much faster than someone who is unfamiliar with, and could possibly damage the equipment. Plus, the tests usually take only a few hours with someone familiar with the equipment, versus a few days for someone who does not work regularly with the equipment.

For high purity gas systems, requirements for the material in product contact closely mirror those of a high purity water system. All new high purity systems should be pressure tested, cleaned, and flushed according to preapproved procedures. For stainless steel lines serving aseptic process areas (downstream of final filters), the weld maps should be matched to the weld logs and to the material certifications. If passivation has been specified, its proper execution and flushing should be verified.

Operational Qualification Issues

As with any system, all critical instruments should be calibrated prior to the performance of operational tests. Critical instruments on a process gas system are those instruments used to measure the parameters listed in Figure 1. However, an instrument need not be permanently installed for each characteristic. For example, if diversity testing is done well, the permanent installation of flowmeter(s) should not be required. But a pressure switch used in maintaining the minimum system pressure by turning on the lag compressor, should be calibrated.

The instruments used to monitor the critical characteristics of a breathing air system should also be calibrated. These include on-line carbon monoxide (CO), carbon dioxide (CO₂), and dewpoint monitors. CO and CO₂ monitors can be easily calibrated by using standardized test gas canisters which trigger the alarms at the appropriate levels. The manufacturer of the respective monitor can usually provide the certified gas canisters. The gases are typically provided in concentrations that correspond to the alert and action alarm levels. They can be easily input to the monitor, and then flushed from the system.

Sequence of Operation Testing

For complex systems, such as multiple air compressors or multiple liquid nitrogen vaporizers, care should be taken to test, or at least bracket, all oper-
ational scenarios. This includes testing each compressor in a lead and lag position.

Backup compressors or gas cylinders should be tested with the rest of the system. All potential operating scenarios should be explored during the operational qualification process. If an operating scenario affects the quality of the gas produced, it should be incorporated into the hydrocarbon, dewpoint, and microbial testing.

**Testing of System Characteristics**

The following sections review specific measurement techniques and issues for each system characteristic listed in Figure 1.

Each measurement technique should be carried out with calibrated instrumentation. Although Draeger tubes and some accessories will not come with NIST certificates, the flowmeter and timer used to capture the sample should be calibrated. The results obtained from accessories, such as Draeger tubes, should be reported with a corresponding error based on the manufacturer’s statement of accuracy. Test results are only as good as the sum of the errors introduced during measurement.

Testing must be performed so that additional error is not introduced into the system. For example, during microbial sampling, an uninformed protocol executor might put the flowmeter between the point-of-use and the agar plate, but this introduces potential additional microbial contamination from the flowmeter. Whenever possible, valves, flowmeters, flow restriction devices and pressure gauges should be placed downstream of the variable being tested. By minimizing introduced errors, the certainty of the final test result is supported.

Test methods should be thoroughly documented, so that qualification can be repeated years after the original tests. For a small start-up company, this may mean simply writing down the test procedure in the comments section of the protocol. For more mature companies that will be routinely performing these tests, the methods should be codified in a company guideline or SOP.

**Pressure**

Although pressure is probably the simplest characteristic to measure for a large system, a bucket full of fittings may be needed to provide connections to all the points of use. Qualification should not be destructive. If the gas lines are already connected to process equipment, the reading from the instruments on the equipment may be obtained, and the line need not be broken.

Nothing should be taken for granted. If there is a pressure or flow specification at a point-of-use, that point-of-use should be tested. One cannot assume that because the correct pressure appears at one drop in a room, it applies to all drops in the room.

Pressure considerations during diversity testing are discussed in the following section.

**Flow**

The flow rate of each point-of-use should be measured to verify that user requirements are met. However, for many drops, there may be no predetermined user requirement. Typically, a baseline flow measurement is taken for each drop, whether or not it has a predetermined specification. By obtaining a flow rate measurement for each use point, a comprehensive document is established, which can be used in the future to help make decisions about whether the system can support a new piece of equipment. For example, if on initial test, only 10 scfm could be obtained, it is clear that the line size or supply pressure will need to be increased to support equipment that requires 25 scfm.

Performing the flow test at each drop also provides a visual check for large pockets of stagnant water in the pipeline. This can be important because dewpoint measurements may not be performed at all locations. Condensate may form in the lines during the initial installation of a system, or after an old portion of an existing system has not been used for an extended period. If water is found in the line, the system may not have been adequately cleaned and flushed.

Flow rate diversity tests should also be performed to identify how many (and which) points-of-use can be operated simultaneously. For a new system, diversity values should be predefined in the design documents. For existing systems, a few interviews with the equipment users should provide sufficient information for educated assumptions about simultaneous use of equipment. Simultaneous recording of flow rate and supply pressure at critical points-of-
use provides very useful information about the ability of the system to perform as designed.

Flowmeters can be found in most process equipment and instrumentation catalogues. A good contract calibration company should be able to calibrate the flowmeter, and provide a standardization table for each process gas.

Purity

If claims are made about the purity of the process gas, then testing should be performed to demonstrate that the appropriate specifications are met. A sample is typically obtained into a vacuum container or bag that can be transported to a laboratory. The methods used to obtain the sample, and to demonstrate purity should be carefully documented and reproducible.

Hydrocarbon

Among the many ways that hydrocarbon tests can be performed, the most common is the use of Draeger, or equivalent, tubes to indicate the approximate level of contamination. These indications are generally not traceable to a standards bureau, such as NIST, but they are a reliable, repeatable, and commonly accepted method for discerning system contamination.

For more reliable, precise data, a gas sample can be obtained for laboratory analysis. This is usually necessary for demonstrating compliance with breathing air standards. Most large contract environmental testing laboratories provide the vacuum containers used to obtain and transport the sample.

Hydrocarbon measurements should be taken near the source during maximum load conditions to ensure that minimum system requirements are met. They should be tested at points-of-use where product will be contacted. Bracketing should be used on large systems to keep the number of tests to a manageable level. For example, in a room with three compressed air drops, a sample from location one on day one, from location two on day two, and location three on day three should be adequate to ensure that portion of the line is hydrocarbon free.

Dewpoint

Dewpoint can be a difficult characteristic to measure. The equipment used to measure dewpoint include chilled mirror, moisture level conversions, and others. The chilled mirror method is usually accurate enough to meet the process requirements. Alternatively, Draeger tubes (or their equivalent) can be used to measure moisture levels in ppm, which can be converted to dewpoint. Additionally, there are handheld measurement instruments that can be submerged in the process gas to provide dynamic measurements.

It is important that the dewpoint measurement be taken at the correct temperature and pressure. The dewpoint conversion information provided by manufacturers is often only applicable at atmospheric pressure and standard temperature. Measurements taken at other pressures and temperatures must be converted to ensure that the system specifications are met. Measurements taken at high pressure can also damage the measurement equipment.

Particulate

Most standard particle counters can be used to measure particulate levels in process gases. The same caution with respect to pressure also applies to particle monitors. The supply gas is limited to very low pressure thresholds. The monitors usually contain their own pump because they are mainly used for collecting samples from room air.

Flow must also be carefully controlled during particulate measurement. Particle counters are usually designed to pull the sample at 0.1 or 1.0 cfm. Most particle counter manufacturers can provide a dispersion tube that can be used to bring the gas down to the required flow and pressure.

The calculations provided in Federal Standard 209E can be used to translate the sample measurement to a specific confidence level for the room clas-
sification being tested. Again, the particulate level should correspond to the particulate level of the room into which the process gas is being exhausted.

**Microbial**

Microbial air samples can also be difficult to obtain. A variety of sampling devices, such as slit-to-agar, centrifugal, and direct impact, can be used. The best method will closely mirror the sampling technique used for open air measurements in your facility.

In recent years, sampling devices have been designed specifically for process gas sampling. A sampling atrium can be used to pull samples directly from the process gas line. The sampling atrium can be sterilized between uses to ensure that it does not add to the microbial load of the sample. An agar plate, such as that used for room air sampling, can be easily and aseptically placed into the atrium for sample capture. The amount of air that passes over the agar plate should match that of a typical room air sample, usually at least 40 liters.

**Post Validation**

After the initial qualification, process gas systems should be maintained in a qualified state. To accomplish this, the following actions should be taken:

- Utilize change control.
- Develop preventive maintenance (PM) and operational SOP’s.
- Calibrate any critical instruments.
- Train mechanics and operators on the SOPs.

Point-of-use filters should be included in a PM program. All point-of-use filters can be changed by maintenance personnel at a specified frequency, such as semiannual. Alternatively, point-of-use filters are considered part of the process equipment that it serves. In this method, production operators are responsible for checking and replacing the filter as part of the equipment setup. The main benefit of this approach is that filters are maintained with the same frequency as the equipment. If equipment is not used, money is not wasted on filters, but if equipment is used frequently, the filters receive a corresponding level of attention.

**Summary**

If it is approached methodically, validation of process gas systems should not be an overwhelming task. The potential impact of the specific system on the product and the process must be considered. Execution of a well-developed plan that demonstrates conformance to the predefined criteria should be simply a milestone on the way to a validated facility.

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**About the Author**

Jeff Hargroves is President of Propharma Group. Hargroves has specialized in the validation of utilities, equipment and processes for pharmaceutical and biological manufacturing facilities. His engineering background includes design and construction management for manufacturing facilities and research and development laboratories.