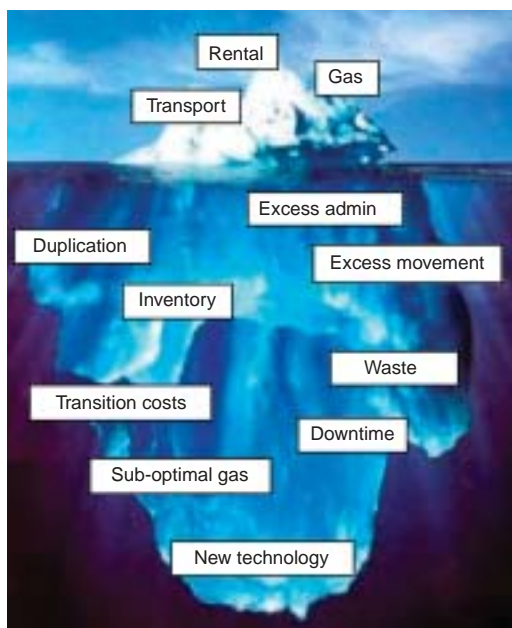


# Establishing and Maintaining An Effective Gas Evaluation and Management Program

Steve Scheuring



Managing gas supplies for pharmaceutical laboratories is a complex task. In this article, the author reviews the process by explaining gas nomenclature, purity levels, and how impurities can affect applications. In addition, the author describes how to minimize contamination risks and reduce costs through proper management of the gas supply.

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When pharmaceutical laboratory managers, chromatographers, and researchers rank their expenditures, gases and cryogenics rarely reach the top 10. Yet when they rank laboratory supplies by how difficult they are to maintain and manage, gases invariably bubble to the top of the list. Gases, whether in liquid or high-pressure form, are difficult to order, store, and use. This article explains some of the reasons for these challenges and suggests several potential remedies.

## Selecting the right gas

Laboratories must select carrier, makeup, and fuel gases for analytical equipment and choose liquid gases to be used as cryogenics for sample storage. Depending on the application, technicians may specify the names and grades of the gases they need. However, often it is not clear what those names mean because, with few exceptions, no industry standards exist for naming gases or grades. Gas grades, specifications, and cylinder size vary from supplier to supplier, and the “300-size, zero-grade helium” offered by one company may be very different from the “300-size, zero-grade helium” offered by another.

Few users realize that most gas-grade names are not regulated. For example, there is no universal standard for defining what constitutes a zero-grade gas. A researcher may assume that *zero-grade helium* means the gas is “five nines” (99.999%) pure. However, a review of published product specifications from gas suppliers’ Web sites reveals that no major specialty gas supplier offers a zero-grade helium that is 99.999% pure. Purities of zero-grade helium range from 99.995 to 99.998% pure, and one company has stopped offering zero-grade helium.

Exceptions to this general rule do exist, especially in the pharmaceutical laboratory. For instance, to call a gas “medical grade,” it must meet certain FDA criteria. A paper trail for the gas cylinder is required, and the gas company is subject to FDA audits. In addition to gases covered by FDA regulations, some gases used in emissions monitoring must meet government standards. Yet these are the exceptions; most gases used in analytical laboratories fall into the general category of gases for which there are no regulations governing their nomenclature. The lack of a universal standard for defining gas grades and names makes the selection of the right gas a complex task.

### Which Nitrogen Would You Choose?

Impurity(ppm)	Supply A	Supply B	Supply C
Oxygen	5	3	1
Argon	NA	NA	4
CO <sup>2</sup>	NA	1	1
CO	NA	1	1
H <sup>2</sup>	NA	NA	1
THC	NA	1	1
Water	5	4	1
Purity	99.999%	99.999%	99.999%

Are these really the same?

**Figure 1:** These nitrogen supplies are all 99.999% pure. However, the differences in their impurities could be important.

Users who select a gas by name alone can end up with inappropriate selections.

Adding to the complexity is confusion surrounding the issue of purity. Many users think they want the purest gas (i.e., gas that is 99.999% pure). If they ever encounter a problem with a laboratory gas, they may demand even higher levels of purity. Instead, they should consider the specific impurity found in the gas.

For example, consider two spoonfuls of sugar, each consisting of nearly pure sugar. One is 99% pure and the other is 95% pure. Given a choice between the two, most people would choose the sugar that is 99% pure. A smart user, however, should know much more than the purity level to make an informed decision. For example, the small percentage of impurity found in the 99%-pure spoonful might be rat poison, and the 95%-pure spoonful's impurity might be salt. Now which one would you choose? It is possible that a gas with a higher purity assay—99% pure—may actually be more detrimental to a user than one with a lower assay of 95% purity. Figure 1 provides an example of this: All three supplies of nitrogen are 99.999% pure, but the impurities in each are different. These differences could be significant.

When users are selecting a gas, they must consider how impurities could affect a specific application. The impurities found naturally in the raw material or introduced during production or filling could give false readings, create baseline noise, or cause other analytical problems. In some cases, impurities also can cause equipment breakdowns that lead to downtime. Two parameters are used to understand impurities. First, one must determine which impurities would cause series problems for the laboratory's application. Second, one must determine the quantity of those impurities that the application can tolerate without hindering analytical results or adding to operating costs.

The three most common contaminants that affect chromatographic applications are oxygen, moisture, and hydrocarbons. Oxygen can accelerate column bleed and affect column life and retention time. In some applications, oxygen also can cause "ghost" peaks. Moisture affects performance in sev-

eral ways: It can cause ghost peaks, affect retention time and base-line noise levels, and shorten column life. Hydrocarbons can affect baseline noise and analyte quantification and can cause ghost peaks. Other contaminants also can affect performance. For example, some mass spectrometry applications are sensitive to inert gases such as krypton even though inert gases do not affect the performance of many other types of detectors. Most detectors also are sensitive to compounds that are similar to the analytes. Electron capture detectors (ECDs), for instance, are sensitive to halogen contamination because ECDs are selective for halogens.

Once users understand the impurities that can affect an application, they then need to select a gas that has the lowest purity level their system can tolerate, which will enable users to produce the desired results at the lowest possible cost. Selecting a gas that is higher in purity than required wastes money without producing a reasonable improvement in performance. For instance, a pharmaceutical company may purchase high-purity helium as a purge gas for liquid chromatography applications even though a lower grade of specialty gas helium would be acceptable. In this case, selecting a higher-grade gas makes no discernable difference in performance and simply adds unnecessary costs to the process.

As a pharmaceutical product approaches commercial approval, some pharmaceutical companies write specific gases into their own standard operating procedures, especially those involved in the production of the drug. Specificity may not be legally required, however, for support gases used in quality control analysis. If companies write procedures specifying a gas-grade name, specification, or paper-trail requirement that is too specific and not necessary for FDA approval, they may limit their options for selecting gas vendors and making purchase decisions in the future. The key is to provide the specificity necessary for FDA approval without hampering the company's ability to improve or change suppliers of analytical gases.

After selecting the right gas for the application, users then must consider two additional issues. First, what is the gas supplier doing to ensure that impurities do not enter the cylinder? Second, what assurances does the supplier provide for the quality of the delivered product?

### Ensuring gas quality

Gas quality must be verified at every step of the process—including raw materials, bulk transfers, cylinder filling, and delivery—to ensure that no part of the supply chain allows for the introduction of impurities.

The most important verification is the final product. Many applications require a certificate of analysis for a gas product supplied in a cylinder, which the supplier must provide. Without this certificate, a user cannot be sure that the cylinder does not contain a contaminant that could affect the process. In other cases, the gas is not required to be individually analyzed as long as it conforms to standards. In such cases, the gas may come with a certificate of conformance. Users should be wary of any supplier that tries to represent a certificate of conformance (a promise to meet a specification) as a certificate of analysis (an actual analytical result). On the other hand, for pharmaceuti-

cal gas applications requiring a paper trail, users should be careful not to be too specific with the certificate request. Dictating the specific format of a certificate of analysis in a procedure may lead to unnecessary custom work by the gas company—work that the gas company will build into the customer's cost.

In addition, if a gas company represents a specification as "typical," it means that the assurance is not tied to a specific analysis. *Typical* in this case means that the company is stating that "more often than not, this gas will meet specifications, but if it doesn't, tough luck."

It is also important to check that the certificate of analysis is for the end-use product in the cylinder, not the raw material. In the majority of cases, problems with gas are related to the gas cylinder's hygiene, not the raw material. The three most troublesome contaminants—oxygen, moisture, and hydrocarbons—are also the contaminants that have the greatest potential to enter a cylinder during the filling process. Examples of these possible contaminant sources include raw material source contamination, hydrostatic testing, gas leakage in the filling process, cylinder service changes, top filling, and zero-cylinder pressure.

**Raw-material source contamination.** The raw material is a less-common source of contamination than often believed. However, a few cases exist in which raw material can affect analytical performance. For example, helium for analytical applications should be sourced from a supply that was at one time liquefied. Although liquefied helium is more expensive, it has a lower potential to be contaminated, because most contaminants are removed during the helium liquefaction process.

Another example is synthetic air for flame ionization detectors (FID). Air supply for an FID should have hydrocarbon levels <1 ppm and even lower levels for low-level analysis. The best way to minimize hydrocarbon content is to purchase a synthetic air blended from liquefied gases.

It also is important to note that air intended for instrumentation will have a CGA 590 valve fitting. Although the proper valve does not ensure that the air is appropriate for the application, an incorrect valve signals a problem. For example, if the air delivered for FID service has a CGA 346 fitting, it is clearly the wrong supply.

**Hydrostatic testing.** Depending on whether it is composed of steel or aluminum, a cylinder must be pressure-tested every 5 or 10 years to ensure its integrity. Usually, a gas supplier will test a cylinder hydrostatically by filling it with water to five-thirds its working pressure to measure expansion. If the cylinder leaks, or does not stretch and then return to normal size, it is discarded. Otherwise, it is stamped and put back into service. When hydrostatically tested cylinders are not properly baked out to remove moisture, moisture contamination can remain. A new technique, ultrasonic testing, does not expose the cylinder to moisture and reduces this potential source of contamination.

**Gas leakage in the filling process.** Although gas suppliers intend for gas filling to be a one-way process, the Venturi effect caused by any leak could allow air, which usually contains ~21% oxygen as well as a lot of moisture and hydrocarbons, into the sys-

tem. Depending on the composition of the local air, the hydrocarbon concentration could be as high as 60 ppm. Suppliers who routinely conduct a prescribed leak check during filling can minimize this potential contamination source.

**Cylinder service changes.** Suppliers sometimes take a high-pressure steel cylinder out of service for one gas, repaint it, and then use it for service with another gas. If the supplier does not follow proper standard operating procedures, these service changes can be a contamination source. For example, if a gas supplier converted cylinders from sulfur hexafluoride ( $\text{SF}_6$ ) service to helium service, typically no problem would arise because both products are considered to be inert. However, if a gas user hooked up a converted helium cylinder to an ECD, the converted cylinder could cause problems because ECDs look for halogens and will detect any residual  $\text{SF}_6$  from the prior service.

The larger a gas company's cylinder fleet, the lower the probability that the supplier will need to change cylinders from one gas service to another. Users can determine whether a company is changing cylinders by checking the paint job on the cylinder. Most companies paint cylinders different colors for different product classes. A cylinder with different undercoats of color showing through the topcoat indicates that the company probably has been changing cylinders from one gas service to another.

**Top filling.** High-pressure cylinders usually are not completely emptied by the user; they are returned to the supplier once they reach a minimum pressure. To reduce raw material costs, some gas companies may fill on top of the residual product in a returned cylinder, especially if the cylinder contains an expensive raw material such as helium. But this shortcut also can introduce contaminants because if the user's operating pressure is higher than the residual cylinder pressure, contaminants from the user's system can enter the cylinder even if there is positive pressure on the cylinder. If the supplier takes the shortcut of filling on top of the residual gas, the next cylinder user may pick up the contaminants from the prior user. Cylinders must be properly cleaned before filling by subjecting them to a systematic purge and evacuation procedure. Another way to minimize this contamination risk is for the gas company to use valves designed to prevent back flow.

**Zero-cylinder pressure.** Another source of contamination arises when a cylinder is bled completely empty. The high upstream pressure can cause liquid-phase contaminants to enter the cylinder. A normal purge and evacuation procedure will remove gas-phase contaminants, but it may not be robust enough to remove liquid-phase contaminants. The only way to remove some liquid contaminants is through a bake-out procedure (if it is not a flammable liquid) or an overnight vacuum. A gas company also must remove the valve on zero-pressure cylinders and inspect for liquid condensation. Customers usually avoid charges for this expensive devalving process by returning cylinders with positive pressure remaining (~100–150 psig). When customers do not return the cylinders this way, the supplier must follow procedures to ensure contaminants are removed.

## Drinking through a dirty straw

If users are sure of the purity of a gas but still are not getting the desired results, they must investigate whether their own on-

### Proper Tubing Can Eliminate Leaks



**Figure 2:** Small molecules such as helium and hydrogen can diffuse through flexible tubing. This photo shows a flexible pigtail pressurized with 2000 psig of helium after 5 min. under water.

site gas delivery systems are introducing impurities, which would be like drinking clean water through a dirty straw. For example, improper piping, regulators, or other equipment in the laboratory can be a source of contaminants. Several general guidelines can be followed to avoid introducing impurities on-site.

First, it is important to use the proper analytical regulators. As a general rule, big is bad. Regulators must have low dead volume and stainless steel diaphragms with packless valves and be lubricant-free. Some regulators on the market labeled “analytical regulator” contain hydrocarbon- or halocarbon-based lubricants, which can affect the analytical performance of FIDs, ECDs, mass spectrometers, and other instruments. In addition, regulators for chromatographic applications must be designed specifically for the service intended. Using a single-stage regulator for a gas chromatography carrier gas, for instance, can lead to analytical errors when the outlet pressure increases during the life of the cylinder.

Second, leaks in the laboratory gas delivery systems must be avoided. Because of the Venturi effect, if gas is escaping, a countercurrent of air—containing oxygen, moisture, and hydrocarbons—may be entering the system. Stainless steel tubing (of the correct type for the specific application) should be used and connections should be minimized. Also, many flexible pigtails are porous enough for small-molecule gases such as helium and hydrogen to diffuse through the pigtail wall, wasting in excess of 10% of the usable gas product (see Figure 2). Therefore, the appropriate pigtails must be used for helium and hydrogen service.

Finally, proper cylinder-replacement procedures must be followed. Many gas users are concerned with oxygen, moisture, and hydrocarbon contamination, yet they introduce air every time they replace a gas cylinder, thereby defeating the purpose

of buying a high-purity gas. Users can minimize the risk of contamination by following proper purge and evacuation procedures during cylinder replacement.

### Managing the gas supply chain

The final source of headaches and hassles associated with gas supplies includes the complexities of managing a gas supply chain that includes returnable rented containers. Once a cylinder is emptied to a minimum pressure, the user must replace the cylinder with a full one and then return the “empty” cylinder to the supplier. In fact, gas is one of the few laboratory supplies that requires a two-way supply chain, which introduces additional challenges.

Many laboratories have difficulty managing cylinder rentals because the actual rental costs fluctuate depending on the end-of-month cylinder balance. If the balance goes up, so does the monthly rental charge. For example, if a company pays \$5 per month per rented cylinder and has an end-of-month balance of 100 cylinders, the company would be invoiced \$500 for cylinder rental. If the cylinder balance increases to 120 cylinders at the end of the following month, the company would be billed \$600. A user’s system that pays on reconciliation to a specific part number may have difficulty managing and interpreting rental items because the amount is not standard each month.

In addition, rental allocation in some laboratories’ operations can be complicated. Most laboratories choose to make flat allocations, in which each user is allocated a set portion of the bill each month. Because this in-house charge is a flat fee and is a relatively low expense, many end users do not actively monitor cylinder balances. They simply want the gas to be available when they need it, much like a utility. The result is that they typically overstock, with most users keeping in excess of a few months’ inventory on-site even though their gas supplier may make deliveries several times a week.

Container rental may not be a significant cost for each end-user, but when added up across an entire complex, the cost (and the potential savings that would result from reducing inventory) can be high. Calculating cylinder turn (the length of time it takes a cylinder to travel through a site) can help identify if overstocking is occurring.

To determine the number of months that cylinders stay at a site, users should divide the number of total units purchased per month into the end-of-month balance. (An end-of-month balance can be found on any monthly rental statement.) For instance, if a user typically purchases 50 cylinders per month and has an average end-of-month balance of 500 cylinders, a cylinder takes ten months to travel through the facility. At a monthly rental rate of \$5 per cylinder, the total rental cost is \$2500 per month or \$30,000 per year. A reduction in cylinder turn from ten months to five months would result in an annual cost savings of \$15,000. Again, if the gas supplier is delivering gases a few times a week, even five months of inventory may be excessive. Many users who calculate cylinder turn are surprised at how long cylinders sit idly in their facility, adding unnecessary costs.

Incremental savings also can be realized by studying cylinder replacement procedures. As already discussed, if a gas supplier maintains good cylinder hygiene and minimizes the pos-

sibilities of cylinder contamination, cylinders can be emptied to as low as 100 psig. However, in some laboratory applications, the unwritten rule is that cylinders are replaced at 500 psig. When operators are asked why they replace cylinders so much earlier than needed, the most common answer is "That's the way we've always done it." Perhaps the user is concerned about running out of gas. This often occurs on Friday afternoons, when users put on fresh cylinders to ensure that they will have enough to last through the weekend. Yet changing cylinders at 500 psig is the equivalent of wasting one usable cylinder for every six cylinders purchased.

For liquid cryogen applications in pharmaceutical research settings, end users may replace liquid nitrogen dewars sooner than necessary to ensure a sufficient cryogen supply for storage units. When end users have years of research stored in a freezer, they cannot afford to run out of liquid nitrogen. Again, they believe that the need to maintain product supply outweighs any product wasted by proactively replacing the dewars.

In both gas and liquid applications, the answer may be to let a properly designed automated gas supply system, rather than the end user, manage the changeover. Newer, easy-to-use gas manifold systems allow cylinders and dewars to be replaced at the lowest-possible pressure or volume and give users an extra measure of security and supply reliability. After a cylinder or dewar runs low, the system will automatically switch to a backup. After a cylinder is switched and the backup is in use, the empty

container can be replaced. The result is that more gas is withdrawn from a container. This also reduces the need for the user to monitor the gases (the automatic switchover does that) while giving the user an extra measure of security. Implementing such a system for gas cylinders may result in the equivalent of one free cylinder for every six purchased. Implementing such a system for dewars has helped some users reduce cryogen waste by as much as 50% without sacrificing secure supply.

Another common practice in biotechnology and pharmaceutical companies is to use carbon dioxide cylinders as a backup to mechanical refrigeration systems. Some companies routinely replace backup cylinders (e.g., once per month or once per quarter) to ensure a fresh gas supply in the event of a refrigeration system failure. Again, the need to protect years of research stored in the refrigeration system is considered far more important than the cost of wasted cryogen. However, this practice is not ideal. Users can avoid having to replace backup cylinders simply by monitoring the amount of carbon dioxide in the cylinders with inexpensive scales. Some companies have saved hundreds or even thousands of dollars without sacrificing peace of mind by switching to this alternative method.

More-efficient gas packaging such as liquid dewars, micro-bulk, or bulk supply modes also can help reduce logistical challenges. Many pharmaceutical and biotechnology companies should examine the inefficiencies in their cryogen supplies (the liquid nitrogen and carbon dioxide used in sample storage).

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Rather than using carbon dioxide cylinders, for instance, users may benefit by switching to higher volumes supplied in a liquid dewar. And many nitrogen dewar users can benefit from converting to even larger microbulk or bulk supply. All of these changes in delivery can minimize manual monitoring of gas usage, unnecessary replacement, and the associated exposure, waste, and extra costs.

For users that have installed bulk nitrogen tanks designed to build pressure for gas applications, laboratory users also can eliminate waste and inefficiencies by ensuring that users do not tap the tank for a "small squirt" of nitrogen, which will cause a large flash loss of nitrogen gas when the liquid is drawn. Users can reduce nitrogen consumption by as much as 30% by separating small-volume applications from the high-pressure bulk system by installing a separate low-pressure dewar or small-container fill capabilities. In addition, users can assess whether they need cylinders for noncryogenic applications and may wish to convert to generated gas, an investment that can yield a monetary returns in as little as a few months.

### Conclusion

To avoid many of the problems associated with gases, users must understand what impurities affect their application and at what levels. Users should ensure that their suppliers take appropriate measures to maintain gas purity and minimize contaminants by avoiding gas leakage during the filling process, minimizing changes in cylinder service, and taking steps to maintain appropriate cylinder hygiene. Users also should be sure that gas companies check the end-use product in the cylinders to ensure the contaminants are at low enough levels.

At the laboratory, gas users need to take similar measures to maintain gas purity. Installing appropriate regulators and tubing and following proper cylinder-replacement procedures will help maintain the gas purity from cylinder to point of use.

In addition to ensuring quality, good management of gas supplies also can reduce gas expenditures. For example, by calculating cylinder turn, companies can identify excess supply that results in unnecessary cylinder rental fees. In addition, installing automated gas manifold systems and evaluating alternative supply modes such as microbulk and bulk can reduce gas waste and cost without sacrificing security or peace of mind.

Gas supplies for the pharmaceutical laboratory can cause many challenges. However, by following the guidelines described in this article, users can avoid many of those difficulties, ensure the quality of the gases they use, and at the same time, minimize costs. **PT**

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