

Process Gases

Second Edition



Process Gas
Generation/
Supply Systems



Compressed
Air Systems



Air and Gas
Distribution
Systems



Control and
Monitoring
Systems



GOOD PRACTICE GUIDE:

Process Gases

Second Edition

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Preface

Gas usage is an integral part of the pharmaceutical industry. Gases are used through various stages of manufacturing for reasons such as for inerting, blanketing, pH control, stability and maintaining product quality to name a few.

This ISPE Good Practice Guide discusses the applications of gases used in pharmaceutical processing and production and provides an overview of the global pharmacopeias and regulations. Recent advances in construction materials and updates on current good practices are presented.

This second edition of the *ISPE Good Practice Guide: Process Gases* is aligned with relevant updates from the EudraLex Volume 4 Annex 1 and Annex 15 revisions along with the latest versions of the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, and the FDA draft Guidance for Industry: Current Good Manufacturing Practice for Medical Gases.

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1 Introduction

1.1 Background

Gas usage is an integral part of the pharmaceutical manufacturing process. For the purposes of this Guide, gases are grouped into two categories: process gases and medicinal gases.

Various types of process gases are used through the different stages of pharmaceutical manufacturing, including production, processing, storage, and transportation. These gases serve a variety of purposes, such as providing inert environments, promoting biological growth processes, and preserving product quality. These gases include, but are not limited to:

- Nitrogen (N₂)
- Oxygen (O₂)
- Argon (Ar)
- Carbon Dioxide (CO₂)
- Compressed Air

These five process gases are the focus of this Guide. There may be other gases used in the future or in current proprietary applications for pharmaceutical processing that are not mentioned in this Guide.

The process gases used in pharmaceutical product production, such as Active Pharmaceutical Ingredients (APIs) and finished dosage forms, play a crucial role in processes such as inerting, blanketing, purging, pH control, and sterilization.

Although process gases do not come into direct contact with patients, they are subject to regulations and GMP to ensure the quality and safety of the final product. The relevant parameters of a gas are determined by a risk assessment, which is used to develop the gas specifications. Gas quality and purity (if necessary) are carefully monitored and controlled to prevent contamination and ensure consistency. Proper handling and storage of gases are also important to prevent accidents and ensure the safety of workers.

Inert gases, such as nitrogen and argon, are commonly used in pharmaceutical manufacturing. Nitrogen provides an oxygen-free environment, essential for the stability and preservation of many pharmaceutical products. Nitrogen is also used in packaging pharmaceutical products to prevent oxidation and moisture absorption, both of which can degrade the quality of the product. Additionally, nitrogen is used as a blanket for pharmaceutical water systems' storage tanks to protect the pharmaceutical water from the environment.

Argon is used in the production of drugs requiring an inert atmosphere, such as the synthesis of certain APIs and filling drug vials.

Oxygen, in controlled amounts, is used in manufacturing products requiring aerobic (oxygenated) conditions, such as for bacteria or yeast fermentation needed in the production of antibiotics and other medications.

Carbon dioxide is commonly used in pharmaceutical manufacturing as it is a versatile gas offering many important applications in biopharmaceutical production from cell culture to sterilization and purification. Carbon dioxide is often used in cell culture bioreactors to regulate the pH of the media.

Clean compressed air is an important utility in pharmaceutical production and is used for a variety of purposes, including instrumentation, process control, cleaning/drying, and packaging. Clean compressed air is critical to the production of high-quality pharmaceutical products as it can ensure that the contaminants in compressed air are at an appropriate level for the intended use, allowing pharmaceutical manufacturers to maintain an environment that minimizes the risk of product contamination and ensures product safety and efficacy.

A medicinal or medical gas is a gas or gas mixture that is intended for direct patient contact, either through inhalation or administration into the body. Examples include oxygen, nitrous oxide, and medical air. These gases are used for various therapeutic purposes, such as anesthesia, respiratory support, and pain relief. Medicinal gases are subject to strict regulations and quality standards to ensure their safety, efficacy, and purity, as they directly impact patient health. An overview chapter on medicinal and medical gases has been added to this revision because of the clause included in the EU GMP Annex 1 update of August 2022 [1]. It states:

"Gases and vacuum systems

6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement."

1.2 Purpose and Objectives

The purpose of the *ISPE Good Practice Guide: Process Gases, Second Edition*, is to document accepted good practices and procedures within pharmaceutical manufacturing applications. The Guide promotes science- and risk-based methods for the design, construction, commissioning, qualification, and routine monitoring/operation processes for gas systems that support production. The Guide is intended to align with current regulations to support a robust, efficient design.

1.3 Scope

This Guide presents considerations for specifications of the physical and quality attributes of gases and focuses on cost-effective engineering approaches and practices used for delivering process gas systems for manufacturing facilities in a timely manner and meeting intended purposes.

Specifically, the Guide addresses the processes used for designing, constructing, commissioning, qualifying, and routine monitoring/operating a process gas system that is regulated by health authorities such as the US FDA and the EMA, taking into consideration other international guidelines and regulations.

Although covered to a lesser degree, a regulatory overview of medical/medicinal gases is found in Chapter 10. An in-depth review of medicinal gases and their uses is beyond the scope of this Guide.

For comprehensive information on sampling of process gases, refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [46].

Breathing air, steam, and combustion gases are outside the scope of this Guide. Similarly, gases used as reactants in API processes are also not discussed.

This Guide is neither a standard nor a regulation. It is not intended to replace governing laws, codes, standards, or regulations applying to facilities of this type. These are mentioned only for completeness and where their impact affects facility, equipment, and utility design relative to GMPs. The use of this document for new or existing facilities, equipment, or utilities is at the discretion of the owner or user.

1.4 Rationale for the Second Edition

The decision to issue the Guide's second edition is the result of recent regulatory developments leading to the incorporation of EU Annex 1 [1] and Annex 15 [2] revisions. In addition, recent advances in construction materials and updates on current good practices are covered. This revision has also been updated to align with the latest versions of the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [3], *ISPE Good Practice Guide: Critical Utilities GMP Compliance* [4], and *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [5].

1.5 Structure of the Guide

1.5.1 Regulatory Requirements and Industry Best Practices

Understanding the regulations and industry best practices that apply when using process gas or clean compressed air is essential for developing user requirements and the design, as well as operating and monitoring such a system.

1.5.2 Development of User Requirements

An explicit set of user requirements is considered key to the cost-effective design of a process gas system. User requirements should be based on the intended use of the gas and focus on the requirements for that gas, allowing the user to develop the optimum design solution and define the requirements for gas supply and use in the process. This Guide provides recommendations for use during the design of the gas system so that the system aligns most closely with process needs.

1.5.3 Design of Process Gas Generation/Distribution Systems

Discussion of the generation, storage, and supply of gas systems includes on-site generation as well as bottles and bulk storage, and gas delivery systems.

1.5.4 Design of Compressed Air Generation Systems

Discussion of the generation of compressed air includes design considerations for compressors, filtration, air receivers, dryers, and related controls.

1.5.5 Design of Compressed Air Distribution Systems

This chapter provides advice on selecting the appropriate materials of construction and fabrication techniques for compressed air distribution systems to ensure that the quality attributes of the compressed air meet specification from the site of generation to the Point of Use (POU).

1.5.6 Design Option – Control and Monitoring Systems

Control and monitoring systems are described for compressed air and gas systems.

1.5.7 Commissioning and Qualification

Commissioning and qualification are critical processes in pharmaceutical manufacturing to ensure the quality and safety of the final product.

The primary function of commissioning is verification that the system meets the documented user requirements and that, since process gas systems are direct-impact systems, the necessary system control strategy has been identified and incorporated into the system. Quality by Design (QbD) is used to verify that the system is fit for purpose and will ensure product quality and patient safety.

Documentation and record-keeping are critical during the commissioning process. All tests and inspections should be documented, and any issues or deviations recorded and addressed.

Qualification is the process of ensuring that the components of the process gas system function correctly and meet defined standards.

Risk assessment and validation are critical during the qualification process. The risks associated with the process gas system should be identified and assessed, and appropriate measures taken to mitigate these risks. Validation or verification using Process Analytical Technology (PAT) should be carried out to ensure that the process gas system is capable of consistently producing a product that meets the required quality standards.

An integrated approach to commissioning and qualification involves conducting the two processes in a coordinated and systematic manner. This approach can improve efficiency and reduce costs by minimizing duplication of effort and ensuring that all aspects of the process gas system are considered.

Further aspects on Good Engineering Practice (GEP) to the commissioning process can be found in the *ISPE Baseline® Guide: C&Q (Second Edition)* [3], *ISPE Good Practice Guide: Critical Utilities GMP Compliance* [4], and *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* [5].

1.5.8 Operation and Maintenance

Guidance on specific requirements for the successful operation and maintenance of gas systems is described in this section.

1.5.9 Comprehensive Overview of Global Regulations for Medical and Medicinal Gases

This chapter reviews the global regulations and pharmacopeias for medical and medicinal gases, highlighting the general differences and commonalities in the pharmacopeias.

1.6 Key Concepts

This Guide promotes a science- and risk-based approach to provide an effective basis for the planning, design, and execution of gas system projects.

The following key concepts are applied throughout this Guide:

1.6.1 Product and Process Understanding

An understanding of the supported process is fundamental to determining system requirements. Product and process understanding is the basis for making science- and risk-based decisions to ensure that the system is fit for its intended use. Efforts to ensure fitness for intended use should focus on those aspects critical to patient safety and product quality. These critical aspects should be identified, specified, and verified.

Systems within the scope of this Guide support the manufacture and preservation of materials used in many applications including, but not limited to, clinical trials, commercial production of API, and final products. For some manufacturing systems, process requirements depend on a thorough understanding of product characteristics and identification of Critical Quality Attributes (CQAs) and related CPPs, which enable process requirements to be accurately defined.

Specifications for the process gas system should focus on critical aspects. The extent and detail of user requirements should be commensurate with the associated risk, complexity, and novelty of the system and, where necessary, control strategies implemented to mitigate unacceptable risk.

1.6.2 Lifecycle Approach within a Quality Management System

Adopting a system lifecycle approach entails defining activities in a systematic way from conception to retirement. This approach enables the optimization of the management control process. The lifecycle should form a fundamental part of the organization's Quality Management System (QMS), which should be maintained up-to-date as new ways of working are developed. (For example, maintenance, calibration, change control, periodic review.)

As experience is gained in system use, the QMS should enable continual process and system improvements based on periodic review and evaluation, operational and performance data, and root-cause analysis of failures. Identified improvements and corrective actions should be implemented following a change management program.

A suitable lifecycle, properly applied, ensures quality and fitness for intended use as well as achieving and maintaining compliance with regulatory requirements.

1.6.3 Scalable Lifecycle Activities

Lifecycle activities should be scaled according to:

- System impact on patient safety, product quality, and data integrity (risk assessment)
- System complexity and novelty (architecture and categorization of system components)
- Outcome of supplier assessment (supplier capability)
- Compliance and inspection risk

Potential business risk also may influence the scaling of lifecycle activities.

The strategy should be clearly defined in a plan and follow established and approved policies and procedures.

1.6.4 Science-Based Quality Risk Management

Quality Risk Management (QRM) is a systematic process for the assessment, control, communication, and review of risks based on clear and documented process understanding, providing focus to ensure patient safety and product quality. Application of QRM enables effort to be focused on critical aspects of a system. ICH Q9 [14] is complementary to QRM and should be referenced and used in conjunction with QRM.

Qualitative or quantitative techniques may be used to identify and manage risks. Controls are developed to reduce risks to an acceptable level. Controls are verified as part of the qualification effort to verify intended fit for purpose. Monitoring appropriate identified controls as part of the product manufacturing control strategy is incorporated into the defined process validation effort and/or periodic review.

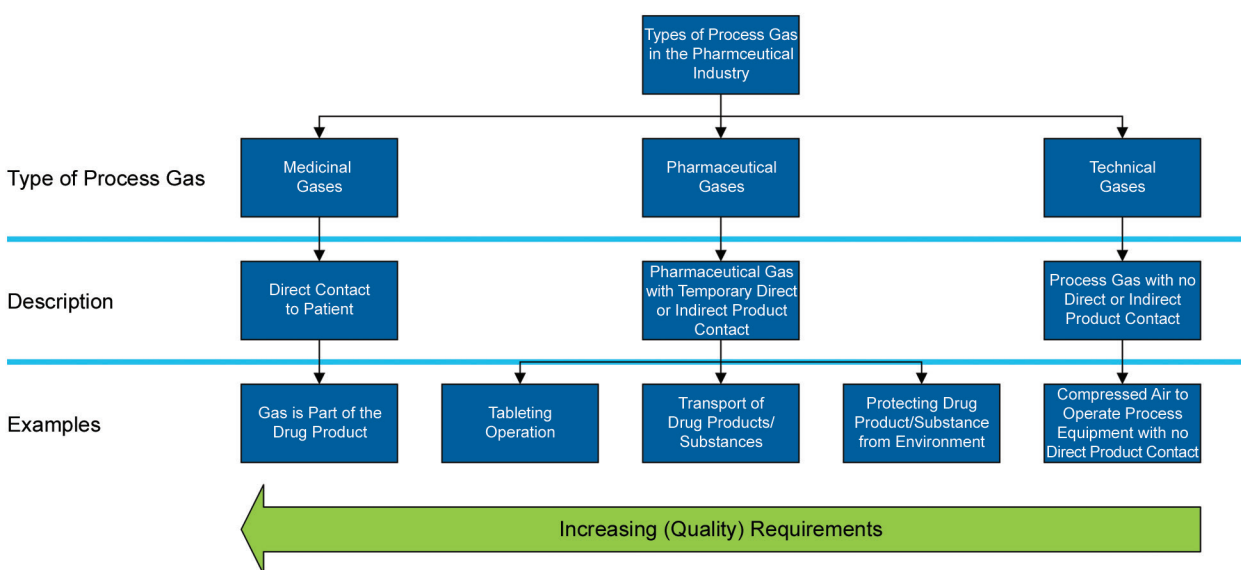
2 Pharmaceutical Gases: Regulatory Requirements and Industry Best Practices

Pharmaceutical process gases and medicinal gases serve different purposes and, accordingly, are subject to different regulatory standards.

It is worth noting that some regulations by EMA or FDA suggest that the specifications for process gases should be based on product or process requirements; the relevance of medicinal gases is not mentioned. However, the US FDA states in the draft Guidance for Industry: Current Good Manufacturing Practice for Medical Gases [6]: “Gases that do not meet the definition of a drug, including gases intended for industrial applications or nondrug medical applications (e.g., a calibration gas used as a standard), are outside the scope of this guidance.”

This chapter presents information pertaining to process gases. See Chapter 10 for an overview of medical gases regulations.

Figure 2.1: Pharmaceutical Gases Overview



2.1 GMP Requirements

2.1.1 European Regulations and Guidance

GMPs in the European Union include several specific requirements for process gases and compressed air:

EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines; Part II – Basic Requirements for Active Substances used as Starting Materials [7]:

“4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.”

EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines; Annex 1 – Manufacture of Sterile Medicinal Products [1]:*“Gases and vacuum systems*

6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.

6.19 Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter should be sterilised. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.”

2.1.2 US Guidance

The FDA has a Guidance for Industry that contains this information on process gases:

FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice [8]

D. Air Filtration, 1. Membrane:

“A compressed gas should be of appropriate purity (e.g., free from oil) and its microbiological and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in purging or overlaying.”

2.1.3 Other Regulations and Industry Guidance

ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients [9]

While ICH Q7 does not specifically address handling the gases used in the manufacturing process, it does provide general guidance on the handling and control of materials. Regardless, the general principles of GMP should be applied to ensure proper gas handling, storage, and use in the manufacturing process.

There are, however, some relevant points from ICH Q7 that can be applied to the handling of gases:

- **Prevention of contamination (Section 4):** Measures should be taken to prevent contamination of the product by gases. This includes proper design and maintenance of equipment, as well as the use of appropriate gas handling procedures.
- **Sampling and testing of incoming materials (Section 7.3):** This section provides context on how a process gas should be released for production purposes.
- **Storage and handling of materials (Section 10):** Gases should be stored and handled in a manner that prevents contamination, mix-ups, and cross-contamination. Proper labeling, storage conditions, and inventory control should be in place.
- **Control of materials (Section 11):** Gases should be sourced from approved suppliers and should meet the required quality specifications. They should be tested and released by the quality unit before use.”

- **Production and in-process controls (Section 12):** The use of gases in the manufacturing process should be controlled and monitored to ensure the quality of the final product. This includes proper calibration and maintenance of equipment, as well as monitoring of critical process parameters.

Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing, Pharmaceuticals and Medical Devices Agency (PMDA) Japan (July 2006) [10]:

The Japanese guidance contains many sections where the use of a process gas is described. The most important gas-related sections are:

“11.2 Routine Monitoring and Control

4. Gases for manufacturing purposes

Gases that may directly contact pharmaceutical products, primary containers, and surfaces that come into direct contact with pharmaceutical products should be periodically inspected and controlled to ensure the absence of microorganisms.”

“13.2.2. Sterilization Equipment

- 5. When materials to be sterilized are not hermetically sealed, gas used for aeration or pressure recovery should be sterilized. Filters used for gas sterilization should have a structure suitable for sterilization and be made of materials resistant to sterilization procedures. In addition, filters should be tested for their integrity to ensure the sterility of gas to be supplied.”*

“15.3 Routine Monitoring and Control

- 4. Filters for sterilizing gas and vent filters for tanks and chambers used in the SIP process should be periodically tested for integrity to ensure that they functioning properly.”*

In addition to these sections, the Japanese guidance contains a separate chapter, Section 17.2 Air and Other Gases, concerning handling of air and other gases.

Summarized, with regards to filtration, the guidance requires that all gases used in a sterile manufacturing process, including compressed air and nitrogen, be filtered through a sterilizing-grade filter with a bacterial-retention capacity of at least 0.2/0.22 µm. The Japanese guidance also requires that the bacterial-retention capacity of the filter be confirmed prior to use, and that the filter is validated to ensure it is capable of consistently achieving the required bacterial-retention capacity.

Filters used in processes in which the filtered gas does not come into direct contact with sterilized products (e.g., air supply during bulk intermediate product manufacturing process and fermentation process) should be controlled by establishing appropriate procedures based on risk analysis.

2.2 Gases Used for Pharmaceutical Production

The clause in EU Annex 1 [1] stating “*where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement*” is important as there are different requirements for gases used in pharmaceutical production processes as compared to medical gases. Therefore, while useful guidance, pharmacopeia medical grade gas monographs most of the time are not appropriate for pharmaceutical production processes. The parameters (especially the purity parameters) and their limits should be defined by the pharmaceutical manufacturer based on a risk assessment of the manufacturing process or product requirements. For example, these monographs from the European Pharmacopoeia (Ph. Eur.) [11] are not applicable:

- Ph. Eur. 1238 Medicinal Air Monograph specifies a limit for oil of $\leq 0.1 \text{ mg/m}^3$, which may be too high for some processes, such as mammalian cell culture (effect growth rate)

- Ph. Eur. 1238 Medicinal Air Monograph specifies a limit of ≤ 500 ppm Volume/Volume (V/V) CO₂, which is not a relevant parameter to measure if the air is being used for ballasting a fluid load autoclave for a terminally sterilized product in a sealed container
- Ph. Eur. 1247 Nitrogen specifies an assay (purity) of $\geq 99.5\%$ V/V. Nitrogen meeting this limit would contain up to 0.5% impurities. This may be inappropriate for a pharmaceutical manufacturing process, where a tighter assay value may be required.

Example specifications for various pharmaceutical applications are described in Appendices 1–3.

It should be noted that the purity profile for gases produced by air-separation techniques, such as nitrogen, oxygen, or argon, are different to those for gases produced by other means, for example, gases extracted from natural gas, such as methane or helium (where the natural gas deposit contains sufficient quantity). In such cases, a wide variety of trace contaminants may be present, depending upon the source of the natural gas and specified gas grade. A much higher grade than would meet the pharmacopeia limits may be required by the manufacturing process.

Gases Used in Sterile Product Manufacturing

The EU Annex 1 [1] states that “*gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate, and microbial quality,*” and that the oil and water content should be specified. The FDA draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [6] states that “*a compressed gas should be of appropriate purity (e.g., free from oil) and its microbiological and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced.*”

Both of these regulations require that the total particle concentration and microbial contamination levels of a gas meet or exceed the quality of the levels specified in the cleanroom or clean air equipment where the gas is used.

The requirements for air quality specified by the EU and the FDA for these environments are detailed in Table 10.2 and Table 10.3 respectively.

It can be seen from comparing the “in-operation” limits in Table 10.2 with the “periods of activity” limit in Table 10.3, that the limits for 0.5 $\mu\text{m}/\text{m}^3$ particle, active air sample, and the settle plate exposure are essentially the same for EU Grades A, B, and C classifications (ISO Class 5, Class 7, and Class 8).

Recognizing these regulatory requirements when conducting the risk assessment to determine the appropriate quality for a process gas used in sterile product manufacturing, the particulate and microbial limits derived from the respective cleanroom classification should be taken into account in defining equivalent limits for the process gas.

In addition to the GMP standards, ISO 8573 [12] classifies compressed air quality by describing its contaminants and provides test methods and analytical techniques for each type of contaminant. The applicability of ISO 8573 is broad, as it is relevant in various industries such as food and beverages, pharmaceuticals, electronics, and automotive.

ISO 8573 Compressed Air [12]

ISO 8573 specifies the quality of compressed air used in various applications. This standard defines the levels of contaminants acceptable in compressed air such as particles, water, and oil. The standard consists of nine parts, and each part deals with a specific aspect of compressed air quality.

- Part 1: Contaminants and purity classes
- Part 2: Oil aerosol content
- Part 3: Test methods for measurement of humidity

- Part 4: Particle content
- Part 5: Test methods for oil vapour and organic solvent content
- Part 6: Test methods for gaseous contaminant content
- Part 7: Test method for viable microbiological contaminant content
- Part 8: Test methods for solid particle content by mass concentration
- Part 9: Test methods for liquid water content

ISO 8573-1, Compressed air — Part 1: Contaminants and purity classes, lists the main contaminants in compressed air supplies as solid particles, moisture, and oil. It identifies quality classes for each parameter. Parts 2 to 9 discuss parameter-specific test methods. ISO 8573-7, Compressed air — Part 7: Test method for viable microbiological contaminant content, includes a test method for microbiological contamination, which is used to determine if there are viable, colony-forming microbiological particles among the solid particles. Part 7 does not specify particular limits for viable microbiological contamination. The limits contained in Part 1 for various air classifications are included in Table 10.4.

The solid particle limits specified in ISO 8573 [12] are different from those specified in the EU and FDA guidance documents [1, 6]. Expressing the particle requirements according to ISO 14644 [13] is the best way to ensure they fit the intended use ensuring the minimum particulate contamination.

ISO 14644 Part 1 [13] is an international standard that establishes the classification of air cleanliness in cleanrooms and associated controlled environments. The standard defines cleanliness levels based on the concentration of airborne particles of various sizes, ensuring that cleanrooms and controlled environments meet the required air quality specifications. It plays a vital role in the area of pharmaceutical gases by providing guidelines for specifying particles sizes and particle limits that could potentially have a negative influence on the cleanroom where the gas used in the manufacturing process.

However, ISO 8573 [12] is a standard commonly referred to by suppliers of compressed air generating systems as a basis for their systems performance specification.

Recognizing that the ISO standards are not directly equivalent and that some parameters are not always relevant to pharmaceutical manufacture, suggested specifications for compressed air and nitrogen gas used in aseptic processing are included in Table 13.1 and Table 13.2.

Note: As stated, the final specification for a particular process gas should always be determined by conducting an appropriate risk assessment of the manufacturing process requirements. For some examples see Appendices 1 to 3.

3 Development of User Requirements

3.1 Introduction

This chapter describes the development of user requirements for a process gas system and provides guidance on how to determine the systems' quality properties (Critical Aspects (CAs), CQAs, and CPPs) within the design space of the process serviced.¹

This chapter follows the principles of the science and risk-based approaches described in ICH Q9 [14] and ASTM E2500-20 [15], as well as EU Annex 15 [2]. The application of risk management and testing is extensively described within the *ISPE Baseline Guide: C&Q (Second Edition)* [3], which should be referenced in conjunction with this Guide.

The user requirement is a foundation document for assisting the use of a QbD approach and considers at a minimum the CQAs, CPPs, and CAs. This process allows the optimization of the system design during the design phase and implementation of a new gas system or revisions to existing systems, allowing the project effort to be focused.

For modification of existing systems, revision of existing user requirements is needed to suit the proposed change, or a user requirement for the change can be produced.

User requirements for a pharmaceutical gas are the specific needs and expectations that the user of the gas has for its quality and performance. The user requirements are often defined as part of the product development process and should be based on the intended use and application of the gas. Pharmaceutical gases can meet different minimum requirements depending on the point of use within the process itself, intensity of contact, composition, form of administration, and indication of the drug product. Pharmaceutical gases that have direct or indirect product contact must also be subjected to different minimum requirements depending on the intensity of this contact but, above all, depending on the composition, form of administration, and indication of the drug product prepared therewith. The specification can only be defined by the user on the basis of process- and product-specific knowledge and within the scope of a risk analysis.

The following sections describe how to evaluate the proper specification for an air/gas system. Examples may be found in Appendices 1 to 3.

3.2 Defining User Requirements for a Process Gas System

The user requirements should minimally contain the qualification/system boundaries and, with that, define the quality requirements on which the system design will be based and the attributes with which the system should comply. In this Guide, the typical classification of CQAs, CPPs, and CAs found in the *ISPE Baseline Guide: C&Q (Second Edition)* [3] are used.

Quality requirements on compressed air or gases may be based on:

- Product
- Process
- Cleanroom classification
- Existing regulations (e.g., monographs if applicable)

¹ Process gases are used during the manufacture of medicinal products. Unlike medicinal gases, they are not medicinal products. Users producing medicinal products who use pharmaceutical gases (see Figure 2.1) must define the requirements based on the intended use of the pharmaceutical gas.

- Other circumstances

Other requirements include:

- Business needs: when the system is installed, scope of supply
- Safety needs: safety requirements at the installation site, noise abatement requirements, siting and adjacency requirements
- Technical needs: operation requirements if power is lost, redundancy requirements, integration with existing automation, use of components
- Environmental needs: energy usage, standby operation

A frequently discussed question is the desired air quality both after purification and at the points of use in a distribution system. This is further described in Section 3.3.

Other requirements necessary for sufficient oversight of the system include:

- Materials of construction
- Design of points of use
- Mode of commissioning
- Desired operating model
- Control strategy

Examples of quality, process, technical, and process requirements are explained in Section 3.3. Appendices 1 to 3 provide examples for the development of a specification and a control strategy for various applications.

3.3 Critical Quality Attributes and Critical Process Parameters or Quality Requirements

User requirements should define (at a minimum) CQAs and/or related CPPs or CAs for the output of the gas system considering the intended use and type of the gas. An example of the considerations to be defined in the user requirements is included in the EU GMP Annex 1, Sections 6.18 and 6.19 [1].

The first step is to clarify which of the attributes of the air or gas system are CAs, CQAs, or CPPs. In other words: is the gas considered an excipient in the final product?

This is answered by how the gas is used, which in turn dictates if it is listed as an excipient in the registration dossier. For example, a gas may be mentioned in a dossier as excipient when the sterile gas is used to overlay the primary container. If the gas overlay in a container takes place but it is not mentioned as an excipient in a dossier, a risk assessment is recommended. This example shows the criticality of the gas used and leads to designating some of the gas quality properties as CQAs or CPPs. An excipient gas typically undergoes a batchwise Quality Control (QC) release, the same as any excipient used in pharmaceutical manufacturing. An example is given in Appendix 3.

However, applications in which a gas is typically not considered an excipient but as a process aid include:

- Tablet manufacturing (e.g., fluid bed granulation or coating)
- Water for Injection (WFI) storage tank overlay with nitrogen

- Pushing a sterile solution through a sterile filter
- Product-contact gases used to manufacture ointments

Some examples of possible CAs, CPPs, or CQAs in gas systems are listed in Table 3.1 (dependent upon process requirements and the potential of the parameter to impact product quality and/or patient safety). Typical examples where these requirements are applicable are found in Appendices 1 to 3.

Table 3.1: Possible Quality Properties in Gas Systems

Quality Properties	Compressed Air	Process Gases
Particles	X ⁽¹⁾	X ⁽¹⁾
Hydrocarbon Levels/Oil Content	X ⁽²⁾	X ⁽³⁾
Microbiology	X	
Moisture Content	X	X ⁽⁴⁾
Purity	X ⁽⁵⁾	X
Impurities according to the relevant monographs	X ⁽⁶⁾	
Pressure	X ⁽⁷⁾	
Notes: 1. A gas that is released in an environment should not negatively influence this room regarding particles load. 2. For example, in case compressed air is used as overlay in a bioreactor and the hydrocarbon level could impact cell toxicity, it could be considered a CA. 3. Might be considered a CA in biotechnological fermentation applications, especially CO ₂ . 4. Could be omitted if proven that no water content can enter the system. 5. Only applicable where the compressed gas source is a cylinder (e.g., not locally generated). 6. If considered an excipient. 7. Only to prevent cross-contamination (backflow), mostly considered a CA.		

Technical Requirements

Technical requirements for a process gas system may include the volume of supply/pressure required at the Point of Use (POU) in the system. For example, modern packaging lines employing high speeds may require elevated pressures to supply enough compressed air per given time frame.

Another example is processing equipment that requires a high volume of air at elevated pressure. Special consideration of this process need may be included in the user requirements.

These kinds of technical requirements could be considered a GEP as well as a GMP aspect of the system, for example, in the simultaneous use of a process gas by several points of use. If too many points are opened at the same time, a significant decrease in pressure or flow may result, which may have a critical impact on the user. Therefore, the pressure (as well as the simultaneous usage) of the gas could be considered a CA for this system as well as a technical requirement in order to operate and create flow through the system by means of a pressure drop.

Organizations may also list health and safety requirements, especially if these are more stringent than the regulations (e.g., noise levels). The responsibility for identifying and complying with these requirements may be left to the designer as the engineer of record.

Technical requirements for an air or gas system may also consist of the choice of materials (Chapter 6), process selection (Chapter 4), POU design (Chapter 6), mode of commissioning (Chapter 8), automation requirements and other engineering requirements.

Business Requirements

Although optional from a regulatory/quality viewpoint, business requirements should be considered as they may be relevant from an operations perspective. During development of the final equipment specifications, the project team should determine whether a business requirement remains within the project's scope. Examples of business requirements include the use of an organization's preferred Programmable Logic Controller (PLC) make and model, instrument vendor, and equipment color.

3.4 Process Requirements

Both existing and potential requirements should be understood before defining user requirements.

User requirements should describe what the system is intended to provide and how it may be used relevant to the requirements of the product and process it serves. Examples of requirements listed in this section are:

- Intended product per system (e.g., single versus multiproduct functionality)
- Process design constraints
- Cleaning/sanitization/sterilization (SIP²) plans per system
- Material handling and integration within the system
- Intended functionality of system components

Note: This Guide bases requirements on product and process needs, and not on available equipment specifications or capabilities.

Practical Examples for Requirements on Process Gases

Examples of process considerations related to user requirements include (see Chapter 4):

Requirements Related to Flow Rate

- Provide consumption rates at POU where applicable. CO₂ or O₂ consumption for pH or Partial Pressure of O₂ (pO₂) control in biotechnological fermentation applications is a typical example (typically a business attribute in those cases).

Requirements Related to Pressure

- Gas required to transfer product
- Clean in Place (CIP) air for assisting system drainage/drying requirements (typically a process attribute)
- Control strategy elements of pressure control as specified and operationally implemented by the engineering and automation design elements
- System instrumentation and alarms (these may be quality or business requirements, e.g., an alarm for high moisture content is a quality alarm. An alarm for high compressor oil temperature is a business attribute).
- Monitoring pressure during system operation

² SIP = Steam in Place

Where supply pressure is critical for the equipment fed from the gas system, it is common industry practice to provide a low-pressure alarm on the equipment feed line. This is considered the most robust approach as it is impractical to monitor the pressure in an entire distribution system, and the local pressure at any point will vary depending on the instantaneous demand on the system.

Requirements Related to Hydrocarbons (Oil Content)

- Hydrocarbons may have a toxic impact in cell culture processes [16]
- Hydrocarbons in oxygen lines may pose a safety risk [17]

A typical system requirement is ≤ 25 ppm or “non-detectable.” The process will determine if a lower value is required, or if this is a CQA.

Requirements Related to Particulate or Microbial Content

- Typically, the specification provided is the same as the “at rest” cleanroom classification of the room into which the gas is to be introduced.
- In some cases, the process or product requirements may be more or less stringent. For example, process contact gas entering a single-use bag may need to be at a higher particulate purity than the surrounding area. Likewise, a nitrogen blanket for a process system that is vented outside the area it is installed in may require a less stringent classification.

Requirements Related to Moisture Content

- These are based on potential needs for adiabatic expansion or dew point of exposed areas. The specification for dew point should not automatically require -40°C unless the process requires it. There is guidance on moisture levels that minimizes the risk of microbial growth within a gas system (see Appendix 5).
- To minimize the potential for promoting corrosion.
- To prevent freezing in lines exposed to cold temperatures.

Requirements Related to Quality and Purity

- Pharmacopeial requirements (e.g., United States Pharmacopeia (USP) [18], Ph. Eur. [11], Japanese Pharmacopoeia (JP) [19])
- Purity requirements should be driven by-product and process needs as defined in regulatory filings.
- In most cases medical grade gases are not required. Medical gases are only for direct use on people or animals (i.e., “breathing air,” see NFPA 99 Standard [20] or the local equivalent).

Other Requirements

- What are the applicable codes and standards for safety?
- Traceability for measuring instruments to national standards
- What are the relevant organizational standards?
- A typical Certificate of Conformance (CoC) states that a supplied gas meets minimal purity specifications, but usually does not include analytical results.

- A typical Certificate of Analysis (CoA) should state the minimal product specifications along with the batch analysis results.

3.5 Equipment Performance/Operational and Maintenance Requirements

The following aspects of system specifications should also be addressed in the user requirements:

System Capacity/Redundancy/Maintenance Strategy

The user requirements may specify the usage pattern and requirement per POU. In large complex systems with diverse applications, the usage patterns can vary significantly and require a more sophisticated approach to pressure control and distribution to accommodate the different needs. On the other hand, simple low volume/use systems typically have more uniform usage patterns that allow for a more straightforward design and pressure management strategy. It is crucial to develop a comprehensive usage pattern for each POU to ensure that the process gas system is designed and optimized to meet the requirements of all applications, regardless of the system's complexity or size.

Redundancy is generally a business necessity, and the user requirements should document the desired level of redundancy for both current and future needs, along with the defined capacity requirements for key unit operations. In clean compressed air generation systems, for example, redundancy involves incorporating multiple systems or components to guarantee uninterrupted and dependable performance, even when one system or component undergoes maintenance, fails, or experiences an outage.

In a typical compressed air generation system, there may be multiple stages of filtration, drying, and compression to produce clean, dry, and high-pressure air. Redundancy can be implemented at different levels of the system, such as redundant compressors, redundant air dryers, redundant filters, or redundant pipelines. Redundancy may also be the availability of an emergency supply providing a backup cylinder pack in case of compressor failure.

The goal of redundancy is to minimize the risk of downtime or interruption to the supply of clean compressed air, which can have a significant impact on the manufacturing process and product quality. Redundancy can also help increase system flexibility and allow for maintenance or repairs to be performed without affecting production.

In addition to hardware redundancy, it is also important to have redundancy in the system design and operation. This can include backup power sources, emergency procedures, and contingency plans to address potential system failures or disruptions.

At the start-up of a project, the overall scope is typically defined in the Project Charter or Project Requirements Brief. This defines the overall scope of the project. Redundancy and capacity issues should already be addressed at this stage, primarily using a business perspective. Based on these agreed project requirements, a design basis is set up on which the project is developed. This design basis leads to issuing one or multiple user requirements to selected vendors to design and fabricate the equipment. These user requirements will include, as appropriate, the previously evaluated and agreed upon documented requirements for redundancy/capacity.

An organization's production schedule and maintenance strategy should also be defined. For example, is maintenance performed outside normal working hours or general maintenance shutdowns (when no equipment redundancy is required) or during working hours (requiring a level of redundancy). Items to consider include:

- Bulk storage – potential to use local canisters/generators to back up a centralized system
- Generation/evaporation
- Primary filtration
- Drying

- Final filtration
- Is a redundant system a requirement or is failure of the system acceptable?
- Is demand fixed or should future expansion of the system be considered?

Cleaning/Sanitization/Sterilization Requirements

There may be requirements for cleaning or sanitization/sterilization of parts of a system (e.g., POU) by means of CIP or Sterilize/SIP, for example, SIP of a final filter immediately prior to the POU process step. There is no industry guidance for these practices specific to process gases. Adoption of cleaning/sanitization/sterilization protocols may be specified by the user when deemed applicable.

Sustainability Requirements

Sustainability requirements include energy recovery and system usage monitoring. Key considerations include:

- Consumption measurement:
 - Energy required
 - Gas or air consumption
- Minimization of pressure losses through the filter elements
- Precise control of pressure losses and pressure regulation; each additional bar represents an increase in power consumption costs
- The implementation of a monitoring system when using several compressors
- Leak detection using mobile measuring equipment or online recording
- Collection and reuse of liquefied CO₂ to reduce the carbon footprint

3.6 Control and Monitoring System Requirements

Control and monitoring systems are designed to provide real-time data on the performance of the system and allow for control and adjustments to be made to optimize system operation. Monitoring systems, either needed or required, can also provide historical and/or trending data.

These systems typically consist of sensors, controllers, and software that work together to monitor system pressure, flow rate, temperature, humidity, and other important parameters.

Specific attributes of the control systems include:

- Monitoring, alarming, sequencing requirements, etc.
- Operator interface requirements
- Connectivity with the existing, monitoring systems/accounting practices, alarming systems

3.7 Facility

Facility requirements should describe the facility area and utilities that the system is intended to operate in or with, such as:

- Required utilities per system as well as units and ranges (minimum, maximum, and normal)
- Ergonomic considerations
- Operator use of system components and operator/equipment interaction
- Skid size limitations
- System location
- Room requirements

Considerations for the intended location for equipment should include:

- Space requirements
- Existing environmental conditions in that space
- Location of the air intake (for clean compressed air generation)

The location of the air intake is important for a clean compressed air generation system because the quality of the compressed air can be impacted by the quality of the ambient air drawn into the system. If the air intake is in an area with high levels of particulate matter, moisture, or other contaminants, these impurities can enter the compressed air system and potentially compromise the quality of the compressed air.

3.7.1 System Segregation Requirements

The user requirements may be used to document agreement on design segregation requirements for systems. As with the system capacity and redundancy requirements, most of the segregation requirements should be addressed and agreed upon at the start of a project. With these decisions made, the approach strategy can be included in the relevant user requirements.

Additional detailed discussion should also occur at the design for impact stage:

- Are separate branches required for process and compressed air?
- Can different branches be classified as GMP or GEP and with that is backflow/cross-contamination an issue?
- Are the individual gases feeding a mixed gas station GMP or GEP?
- Which process parameters should be monitored for a GMP system versus those monitored for a system classified as GEP?

3.8 Reference Documents

It is essential to ensure relevant documents are contained in the user requirements, including documents that may affect the user requirements or related documents. Additionally, documents referenced as requirements in the regulatory section should be available, such as site drawings, company specifications, etc.

3.9 Roles and Responsibilities

The following roles are required, at a minimum, for the review and approval of the process gas user requirements:

System Owner

- Responsible for the identification and specification of business area and end-user needs
- Responsible for the identification and specification of intended uses of the system
- Responsible for reaching and maintaining the validated state

Technical Expert/Subject Matter Expert (SME)

- Responsible for the identification and specification of technical requirements and constraints
- Ensures assets are ready for their intended use. (This role may include, in part or in their entirety, performing validation tasks.)

Quality Assurance (Regulatory Compliance)

- Responsible for ensuring that the product/process requirements and regulatory requirements are correctly specified
- Responsible for verifying that activities and documentation follow applicable site procedures

In addition to these roles, the following might be required for review and/or approval of the process gas user requirements. These roles may depend on the gas application or the manufacturer's organizational structure.

QC

- Responsible for the sampling, analysis, and release of process gases if considered an excipient

Validation

- Ensures that requirements cover the needs for validation testing. (This role may include, in part or in their entirety, performing validation tasks.)

Other SME Functions

- SMEs, other than those listed above, may be required to help link requirements to product CAs, CQAs, and CPPs. These include automation, research and development, safety, etc. related roles.

4 Design Options – Process Gas Generation/Distribution Systems

4.1 Introduction

This chapter covers:

- Applications of process gases
- Gas definitions and properties
- Manufacturing considerations
- Handling and safety considerations

Compressed Gases

The term compressed gases refers to gases that are compressed to a pressure higher than atmospheric pressure, typically stored in a container such as a cylinder or tank.

In the US, compressed gases are defined by the Occupational Safety and Health Administration (OSHA) [21] and classified into different hazard classes based on their physical and chemical properties, and potential health and safety hazards. These hazard classes include flammable gases, non-flammable gases, poisonous gases, and corrosive gases.

A compressed gas is defined in 29 CFR 1910.1200 B.5 [22], (commonly known as the OSHA Hazard Communication Standard (HCS or HAZCOM)), as:

- Gases under pressure are gases contained in a receptacle at a pressure of 200 kPa (29 psi) (gauge) or more
- Gases which are liquified or liquified and refrigerated.

Gases under pressure include compressed gases, liquefied gases, dissolved gases, and refrigerated liquefied gases. The classifications are shown in Table 4.1.

Table 4.1: OSHA 29 CFR 1910:1200 B5.2 Table B.5.1 [22]

Group	Criteria
Compressed Gas	A gas which when under pressure is entirely gaseous at -50°C (-58°F), including all gases with a critical temperature ⁽¹⁾ $\leq -50^{\circ}\text{C}$ (-58°F).
Liquefied Gas	A gas which when under pressure is partially liquid at temperatures above -50°C (-58°F). A distinction is made between: (a) High-pressure liquefied gas: A gas with a critical temperature ⁽¹⁾ between -50°C (-58°F) and $+65^{\circ}\text{C}$ (149°F); and (b) Low pressure liquefied gas: A gas with a critical temperature ⁽¹⁾ above $+65^{\circ}\text{C}$ (149°F).
Refrigerated Liquefied Gas	A gas which is made partially liquid because of its low temperature.
Dissolved Gas	A gas which when under pressure is dissolved in a liquid phase solvent.
Note: 1. The critical temperature is the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression.	

In Europe, gases under pressure are defined in Regulation (EC) No. 1272/2008 – classification, labelling and packaging of substances and mixtures (CLP) [23], Section 2.5.1.1:

“Gases under pressure are gases which are contained in a receptacle at a pressure of 200 kPa (gauge) or more at 20°C , or which are liquefied or liquefied and refrigerated. They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.”

They are subsequently classified according to their physical state when packaged into one of four groups, as shown in Table 4.2.

Table 4.2 European Norm 1272/2008 Table 2.5.1 [23]

Group	Criteria
Compressed Gas	A gas which when packaged under pressure is entirely gaseous at -50°C ; including all gases with a critical temperature $\leq -50^{\circ}\text{C}$.
Liquefied Gas	A gas which, when packaged under pressure, is partially liquid at temperatures above -50°C . A distinction is made between: (i) high-pressure liquefied gas: a gas with a critical temperature between -50°C and $+65^{\circ}\text{C}$; and (ii) low pressure liquefied gas: a gas with a critical temperature above $+65^{\circ}\text{C}$.
Refrigerated Liquefied Gas	A gas which when packaged is made partially liquid because of its low temperature.
Dissolved Gas	A gas which when packaged under pressure is dissolved in a liquid phase solvent.

In the pharmaceutical and biotechnology industries, compressed gases typically fall into one of two categories, liquefied and non-liquefied gases, depending upon their inherent physical state under pressure and their range of boiling points.

When specific elements become liquefied at extremely low temperatures, they are referred to as cryogenic liquids.

Gases may form an unlimited number of mixtures or compounds, with air being the most common example.

Carbon dioxide is an example of a liquefied gas that also has unique physical characteristics in that it may exist as a gas, liquid, or solid simultaneously at its triple point, which occurs at -69.9°F (-56.6°C) and 75.13 psi (518 kPa).

4.2 Process Gases: Descriptions and Properties

4.2.1 General Properties and Characteristics of Process Gases

Table 4.3 presents the general properties and characteristics of the atmospheric gases (nitrogen, oxygen and argon), carbon dioxide, and compressed air.

Note: In Chapter 4, compressed air refers to compressed air supplied in high-pressure cylinders, not compressed air generated on site. For details on compressed air generated on site, see Chapter 5.

Table 4.3: General Properties and Characteristics

Chemical Name	Nitrogen	Oxygen	Argon	Carbon Dioxide	Air, Compressed ⁽¹⁾
Chemical Formula	N ₂	O ₂	Ar	CO ₂	N/A ⁽²⁾
Appearance/Color	Colorless Gas	Colorless Gas Bluish Liquid	Colorless Gas	Colorless Gas	Colorless Gas
Odor	None	None	None	None	None
Molecular Weight (g/mol)	28.01	32.00	39.95	44.01	28.96
Boiling Point	-195.8°C (-320.4°F)	-183.0°C (-297.3°F)	-185.9°C (-302.5°F)	N/A	-194.33°C (-317.8°F)
Sublimation Point	N/A	N/A	N/A	-78.5°C (-109.3°F)	N/A
Critical Temperature	-147.1°C (-232.7°F)	-118.6°C (-181.4°F)	-122.3°C (-188.1°F)	31.0°C (87.9°F)	N/A
Relative Density, Gas (air = 1) at 20°C (68°F) and 1 ATM	0.97	1.11	1.39	1.53	1.0
Solubility mg/l water at 20°C (68°F) and 1 ATM	20	39	61	2000	8.2
Notes: N/A = Not Applicable 1. Compressed air is included in this table as it may be provided in high-pressure gas cylinders. For compressed air generated on site, refer to Chapter 5 in this Guide. 2. Compressed air does not have a chemical formula.					

Note: For additional and comprehensive physical and chemical properties of atmospheric gases, carbon dioxide, and compressed air, refer to:

- Safety Data Sheets (SDS)
- Compressed gas industry publications (e.g., Compressed Gas Association (CGA) [24], European Industrial Gases Association (EIGA) [25])
- Pharmacopeia (e.g., USP [18], Ph. Eur. [11], JP [19], Chinese Pharmacopoeia (ChP) [26])



4.2.2 Process Gas Sources and Manufacturing Considerations

Nitrogen, oxygen, and argon are naturally occurring elements. The earth's atmosphere is composed of approximately 78.09% nitrogen, 20.95% oxygen, and 0.93% argon by volume at sea level. Oxygen supports combustion, and materials that burn in air, such as polymeric filters, will burn vigorously in an oxygen-enriched atmosphere. Nitrogen and argon are considered chemically inert.

Bulk nitrogen, oxygen, and argon are manufactured by fractional distillation of liquefied air. A manufacturing facility that processes liquefied air is commonly referred to as an air-separation unit. Other manufacturing methods of gases include electrolysis, molecular sieve separation, and chemical reactions.

Figures 4.1 and 4.2 show the major process steps that occur in an air-separation unit. The first step is to compress and liquify the air as shown in Figure 4.1. Once liquefied, the air is fed into a double column, shown in Figure 4.2, where counter current distillation is used to produce high-purity nitrogen and high-purity oxygen. In some instances, an air-separation unit has an additional column(s) to allow for simultaneous production of high-purity argon (not shown in figures below).

Figure 4.1: Air Liquefaction Process

Used with permission from Linde Engineering, www.linde-engineering.com.

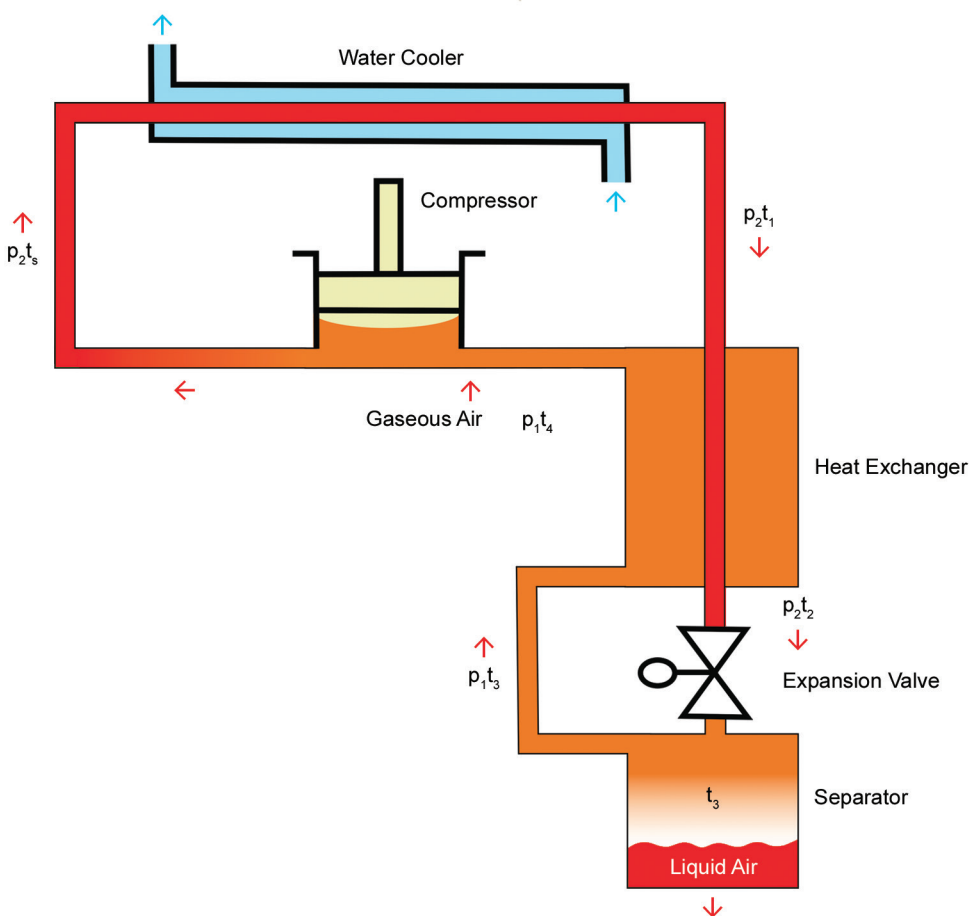
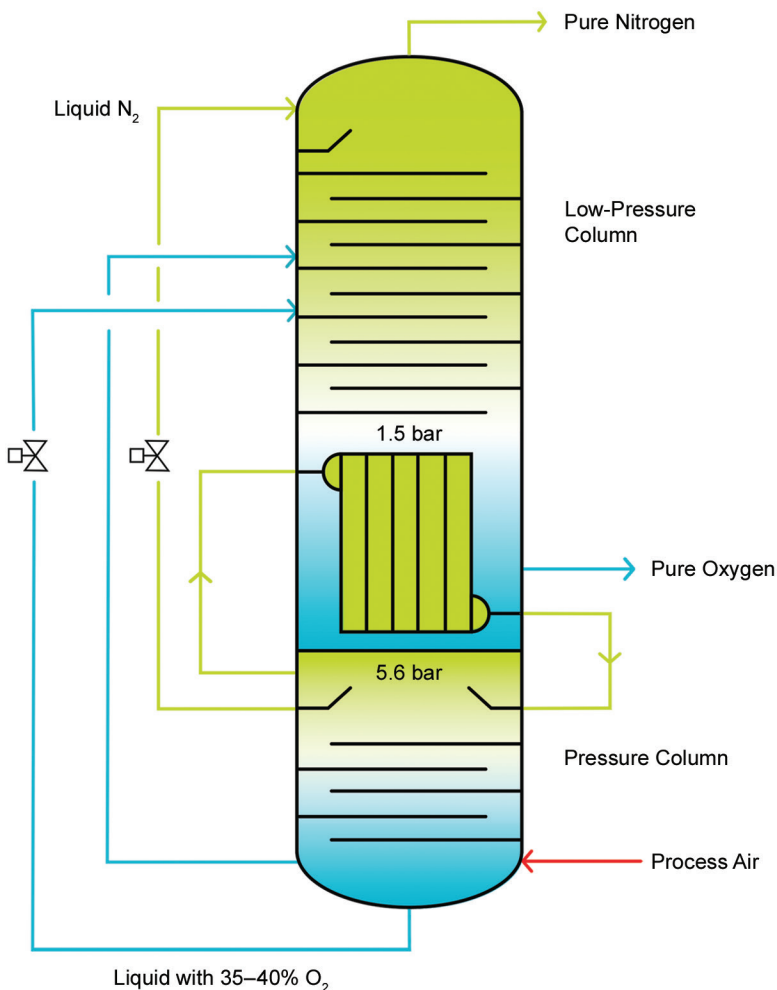


Figure 4.2: Simultaneous Rectification (Counter Current Distillation) of N_2 and O_2
Used with permission from Linde Engineering, www.linde-engineering.com.



Additionally, oxygen and nitrogen can be generated in smaller volumes via the use of on-site oxygen or nitrogen generators. Utilization of these systems to generate high-purity gases on site can eliminate the need for bulk cryogenic storage tanks or high-pressure gas cylinders.

Nitrogen can be generated on-site using membrane-based technology in which a semi-permeable membrane separates nitrogen from the other gases in compressed air. The membrane allows nitrogen to pass through while blocking the passage of other gases, such as oxygen, water vapor, and carbon dioxide. The efficiency of the membrane depends on the size of the pores and the pressure difference across the membrane. Nitrogen generators that use this technology are simple, reliable, and require little maintenance. They can produce low to medium volumes of nitrogen with purity levels ranging from 95% to 99.9%. A unit consists of an air compressor, filters, pre-heater (if required), membrane cartridges, piping, valves, and the control system.

The adsorption process used for generating nitrogen utilizes Pressure Swing Adsorption (PSA) to separate nitrogen from other gases in the air. The process involves passing compressed air through a bed of adsorbent material, such as activated carbon or zeolite, that selectively adsorbs oxygen and other impurities, allowing nitrogen to pass through. The bed is then regenerated by reducing the pressure, releasing the adsorbed gases. Nitrogen generators that use this technology are more complex than membrane systems but can produce high-purity nitrogen with levels higher than 99.999%. The capacity of PSA nitrogen generators ranges from a few cubic meters per hour to several hundred cubic meters per hour. To provide a continuous supply of nitrogen, a twin bed design is required where one

adsorber is in the production phase while the other is regenerated by evacuating the pressure to the atmosphere. The performance of a PSA unit depends on the ambient temperature. The required purity and product pressure have an influence on the air demand and energy consumption.

Oxygen generation by filtration typically uses specialized filters that separate oxygen molecules from other gases present in the air. These filters selectively capture oxygen molecules and release other gases, such as nitrogen and argon. The PSA process for oxygen is identical to the technology used for nitrogen as described above except the adsorbent material has a high affinity for nitrogen, argon, and other gases, but a lower affinity for oxygen.

Oxygen generation by filtration is commonly used in applications where a steady supply of oxygen is needed, such as in medical facilities, laboratories, and for industrial processes. It is a safe and reliable method of generating oxygen that does not require the use of chemicals or high temperatures, making it an environmentally friendly option.

The current requirements for the pharmacopeia monographs for Ar, CO₂, N₂, and O₂ are shown in Tables 4.4 to 4.7 and, as noted, not all pharmacopeias have a monograph for each of the listed gases. Gas availability may be geographically limited as these are purchased materials and not typically generated on-site as in the case of other raw materials (e.g., WFI). For example, finding Ph. Eur. quality gases in the US may be difficult, if not impossible. However, the available gas qualities meet all the requirements of the USP specifications.

Table 4.4: Pharmacopeia Requirements for Argon

Argon (Ar)				
	USP	Ph. Eur.	JP	ChP
Molecular Weight	No Official Monograph in USP-NF 2023, Issue 2	39.95	No Official Monograph in JP 18	No Official Monograph in ChP 2020
Appearance		Colorless gas		
Solubility		At 20°C and at a pressure of 101 kPa, 1 volume dissolves in about 29 volumes of water		
Odor		N/A		
Density		N/A		
Purity		≥ 99.995% by volume		
Oxygen		≤ 5 ppm		
Total Impurities (O ₂ , N ₂ , CH ₄)		≤ 40 ppm		
Water		≤ 10 ppm		
N/A = Not Applicable				

Table 4.5: Pharmacopeia Requirements for Carbon Dioxide

Carbon Dioxide (CO ₂)				
	USP	Ph. Eur.	JP	ChP
Molecular Weight	44.01	44.01	44.01	44.01
Appearance	N/A	Colorless gas	Colorless gas at room temperature	Colorless gas
Solubility	N/A	At 20°C and at a pressure of 101 kPa, 1 volume dissolves in about 1 volume of water	A 1 mL volume of Carbon Dioxide dissolves in 1 mL of water, and the solution is slightly acid.	A 1 mL volume of Carbon Dioxide dissolves in 1 mL of water
Odor	N/A	N/A	Odorless	Odorless
Density	N/A	N/A	1000 mL of Carbon Dioxide at 0°C and under a pressure of 101.3 kPa weighs 1.978 g	N/A
Purity	≥ 99.0% by volume	≥ 99.5% by volume	≥ 99.5% by volume	≥ 99.5% by volume
Nitrogen Dioxide	≤ 2.5 ppm	N/A	N/A	N/A
Nitrogen Dioxide + Nitrogen Monoxide	N/A	≤ 2 ppm Total	N/A	N/A
Ammonia	≤ 0.0025%	N/A	N/A	≤ 0.0025%
Hydrogen Sulfide	≤ 1 ppm	≤ 1 ppm	N/A	≤ 0.0001%
Nitric Oxide	≤ 2.5 ppm	N/A	N/A	N/A
Carbon Monoxide	≤ 0.001%	≤ 5 ppm	N/A	≤ 0.0005%
Sulfur Dioxide	≤ 5 ppm	≤ 2 ppm	N/A	≤ 0.0002%
Water	≤ 150 mg/m ³	≤ 67 ppm	N/A	≤ 0.0067%
Acidity	N/A	N/A	N/A	Pass
Phosphine	N/A	N/A	N/A	≤ 0.00003%
Hydrocarbon	N/A	N/A	N/A	≤ 0.0020%
N/A = Not Applicable				

Table 4.6: Pharmacopeia Requirements for Nitrogen

Nitrogen (N ₂)				
	USP	Ph. Eur.	JP	ChP
Molecular Weight	28.01	28.01	28.01	No Official Monograph in ChP 2020
Appearance	N/A	Colorless	Nitrogen is a colorless gas at room temperature and under atmospheric pressure	
Solubility	N/A	At 20°C and at a pressure of 101 kPa, 1 volume dissolves in about 62 volumes of water and about 10 volumes of ethanol (96%)	1 mL of Nitrogen dissolves in 65 mL of water and in 9 mL of ethanol (95) at 20°C and at a pressure of 101.3 kPa	
Odor	No appreciable odor is discernible	Odorless gas	Odorless	
Density	N/A	N/A	1000 mL of Nitrogen at 0°C and at a pressure of 101.3 kPa weighs 1.251 g	
Purity	≥ 99.0% by volume	≥ 99.5% by volume	≥ 99.5% by volume	
Carbon Dioxide	N/A	≤ 300 ppm	N/A	
Carbon Monoxide	≤ 10 ppm	≤ 5 ppm	N/A	
Oxygen	≤ 1.0%	≤ 50 ppm	N/A	
Water	N/A	≤ 67 ppm	N/A	
N/A = Not Applicable				

Table 4.7: Pharmacopeia Requirements for Oxygen

Oxygen (O ₂)				
	USP	Ph. Eur.	JP	ChP
Molecular Weight	32.00	32.00	32.00	32.00
Appearance	N/A	Colorless gas	Oxygen is a colorless gas under atmospheric pressure	Colorless gas
Solubility	N/A	At 20°C and at a pressure of 101 kPa, 1 volume dissolves in about 32 volumes of water	1 mL of Oxygen dissolves in 32 mL of water, and in 7 mL of ethanol (95) at 20°C and at a pressure of 101.3 kPa	Soluble in 7 volumes of ethanol and 32 volumes of water at 20°C under normal atmosphere pressure
Odor	N/A	N/A	Odorless	Odorless
Density	N/A	N/A	1000 mL of Oxygen at 0°C and at a pressure of 101.3 kPa weighs 1.429 g	N/A
Purity	≥ 99.0% by volume	≥ 99.5% by volume	≥ 99.5% by volume	≥ 99.5% by volume
Carbon Dioxide	≤ 300 ppm	≤ 300 ppm	N/A	≤ 0.01%
Carbon Monoxide	≤ 10 ppm	≤ 5 ppm	N/A	Pass
Water Vapor	N/A	≤ 67 ppm	N/A	N/A
Acid/Alkalinity	N/A	N/A	N/A	Pass
N/A = Not Applicable				

O₂ Note: Where air liquefaction is used to produce O₂, and the O₂ is labeled that it is produced by air liquefaction, based on the requirements in the current USP monograph for Oxygen, the impurity tests (CO₂ and CO) are not required.

Liquified atmospheric gases may be delivered to users and cylinder packaging operations in specialized, vacuum-insulated trailers. Cylinder packaging operations process the gases into returnable liquid containers and high-pressure cylinders of various sizes. The liquid containers and cylinders are delivered to users.

CO₂ occurs naturally in the atmosphere in small quantities; as of 2021 this level stands at approximately 400 ppm (according to climate changes observations [27]). However, CO₂ may be found in larger concentrations as a by-product in chemical refining and fermentation processes. Bulk production of liquid carbon dioxide requires source capture of a feedstock followed by purification and, ultimately, air liquefaction.

Carbon dioxide feedstock is pre-purified from a variety of sources, including:

- Chemical refining processes

- Ammonia production
- Ethyl alcohol production
- Fermentation processes
- Coal powered electrical plant combustion

Carbon dioxide purity levels are typically greater than 99.5% and meet or exceed those required by the relevant pharmacopeia monographs.

Liquid carbon dioxide is normally delivered to customers and cylinder packaging operations in specialized, insulated trailers. Cylinder packaging operations process the gas into dry ice (solid carbon dioxide) and returnable liquid containers and high-pressure cylinders of various sizes. The liquid containers and cylinders are delivered to customers and other POUs.

4.3 Process Gases: Typical Applications

The biopharmaceutical and life science industries use compressed gases in a wide range of applications. The examples below are intended to provide typical cases found in the pharmaceutical and biotechnology industries. In a pharmaceutical quality system as defined in ICH Q10 [28], the pharmaceutical company is responsible for implementing processes to ensure the quality of purchased materials. These processes include the principles of QRM as covered in ICH Q9 [14]. Additional details can be found in the ICH guidelines.

Nitrogen

Nitrogen is most often used as an inert gas for the conditioning of pharmaceutical products in storage and transportation. In specific applications, argon or carbon dioxide is used instead. Nitrogen, argon, and carbon dioxide are also used during the manufacture of APIs and in the production of finished pharmaceutical products.

Nitrogen is used for inerting tanks or other process equipment to minimize the risk of fire, dust explosions, and other explosions by creating atmospheres with low concentrations of oxygen. Three common methods of inerting are purging pipelines, blanketing tanks or other process equipment, and sparging tanks or other process equipment.

Additionally, nitrogen may be used for products sensitive to humid air or oxygen. Moreover, nitrogen is utilized for products that are sensitive to humidity or oxygen exposure. This inert gas serves to replace humid air or explosive solvent vapor in the headspace of contained batches and acts as a blanket in bioreactors, substituting oxygen for anaerobic fermentation processes. The headspace condition can be maintained through blanketing, where nitrogen is supplied to prevent fluctuations in headspace pressure from causing ambient atmosphere ingress, or by sweeping, a process in which nitrogen displaces humid air, explosive solvent vapor, or oxygen during anaerobic fermentation.

For WFI or Purified Water storage tanks, nitrogen blanketing, although not used widely, may be used to reduce changes in conductivity associated with dissolved carbon dioxide.

Liquid nitrogen is used for ultra-low temperature storage (e.g., for cell banking activities where seed banks are stored) in a cryostat, and for backup cooling systems for ultra-low temperature freezers. Cryopreservation, storage of biological materials at very low temperatures, is used to ensure the survival of living cells and organisms. The cells can be stored either submerged in liquid nitrogen or in contact with the cold vapor phase of nitrogen.

Additional uses for nitrogen are:

- Pneumatic systems

- Calibration for dissolved-oxygen probes (0% oxygen)
- Single-use bag inflation and leak testing

Argon

Argon is most used as an inert gas for conditioning pharmaceutical products in storage and transportation and for tank blanketing applications. In some situations, such as in high-purity welding of hygienic piping, argon is used instead of nitrogen. Because argon has a higher density than either air or nitrogen, it is more effective at displacing oxygen (resulting in cleaner welds).

Oxygen

The primary use of oxygen in the pharmaceutical and biotechnology industries is in fermentation and cell culturing processes. In these processes, oxygen is used to improve productivity and cell growth intensity and viability. A high concentration of oxygen up to 100% air may be applied. Where concentrated oxygen is utilized, special care must be taken to ensure piping and equipment are properly cleaned for oxygen service (e.g., removal of oils, grease, and other hydrocarbons). The technical implementation of gaseous oxygen blending in cell culture processes is usually done by mixing gaseous oxygen and air from the usual pressure line by means of special devices (e.g., mass flow controllers), followed by sterilizing gas filtration in front of the bioreactor. Additionally, exhaust and vent filters around the bioreactor may be exposed to elevated oxygen concentrations.

Filtration of oxygen is a significant safety concern as it leads to accelerated oxidation and corrosion of plastics as well as spontaneous combustion. Because thinner filter components, such as nonwoven support and drainage layers, are much more vulnerable to such oxidation effects, it is recommended to use filters that contain more oxidation-resistant materials (e.g., polyaramid nonwoven layers) instead of the relatively fast degradable and flammable polypropylene nonwoven layers found in typical air sterilizing Polytetrafluoroethylene (PTFE) membrane filters.

Besides these degradation effects, oxygen flow builds up static charges on filter media surfaces that can lead to spontaneous discharge with the risk of ignition of degraded organic traces and flammable filter components. This may be followed by combustion and fire generation inside pipes and filter housings. In some locations, filter installations for gaseous oxygen need to be approved by special authorities for plant and operator safety.

Because of these risks, a single-use mode of sterilizing gas filters together with a minimum oxygen concentration for the duration of the fermentation cycle is recommended, in addition to general safety guidelines regarding oxygen handling.

Additional uses for oxygen include:

- Cell cultivation
- Mammalian culture and fermentation
- Ozone generation

Carbon Dioxide

CO₂ is used with incubators in the production of biopharmaceuticals and in the cultivation of mammalian cells.

Supercritical Fluid Extraction (SFE) is where a Supercritical Fluid (SF) is used as a solvent. At critical temperatures and pressures, SFs possess the properties of both the liquid and gas, with density values similar to those of liquids and flow properties similar to those of gases; thus, they are labeled as fluids. The most widely used SF gas is CO₂.

The most common uses for CO₂ include:

- Mammalian culture and fermentation (e.g., pH control)
- Cell cultivation in an incubator
- Freezing and chilling

4.4 Safe Handling and Storage of Gases

4.4.1 Source Gas Distribution and Storage

4.4.1.1 Liquid Argon, Carbon Dioxide, Nitrogen, and Oxygen Storage Vessels and Installations

Argon, carbon dioxide, nitrogen, and oxygen are typically supplied to the end user in either liquid or gaseous forms by one or more of the following means:

- On-site liquid storage vessel
- Transportable liquid containers (e.g., Dewars)
- High-pressure cylinders and manifolds
- On-site gas generation systems

Storage Vessels

Storage vessels for liquid argon, carbon dioxide, nitrogen, and oxygen are commercially available in multiple formats including:

- Portable storage tanks on wheels (e.g., Dewars), with capacities ranging from 49 to 61 US gallons (185 to 230 L) water capacity
- Microbulk tanks, with capacities ranging from 61 to 1,850 US gallons (230 to 7,000 L) water capacity
- Bulk tanks, with capacities ranging from 1,640 to 15,520 US gallons (6,280 to 58,750 L) water capacity

The various formats and sizes are available in different pressure ratings based on the applications and needs of the end user. Portable storage tanks (e.g., Dewars) are generally available in two pressure ratings, 22 psi (152 kPa) and 230 psi (1586 kPa). Microbulk and bulk storage tanks are available in several different pressure ratings between 175 psi (1207 kPa) and 500 psi (3447 kPa).

The storage vessels may be vertical or horizontal depending upon the site and consumption requirements, with the vertical being most common. It is important to consider the storage vessel Normal Evaporation Rate (NER) when sizing a bulk system. NER varies based on tank pressure, tank size, the type of gas stored, and the outside temperature.

Liquid storage vessels have three basic components:

- Inner pressure vessel
- Outer vessel
- Insulation

Inner Pressure Vessel

An inner pressure vessel is usually made of stainless steel or other materials with favorable strength characteristics when exposed to cryogenic temperatures.

The inner vessel of the storage tank is typically designed to sustain a maximum allowable working pressure of 250 psi (1724 kPa). Vessels may be fabricated for higher or lower working pressures depending upon the gas application. The service pressure of the vessel is adjustable using pressure regulators.

To protect the inner vessel from over-pressurization, the storage tank is typically equipped with dual pressure relief valves and rupture disks. Pressure relief valves open when pressure in the inner container rises above a predetermined level. These spring-loaded valves close automatically after relieving excess pressure and do not operate again unless there is a subsequent pressure rise. Rupture disks are thin metal membranes designed to rupture at a prescribed pressure above the pressure relief valve setting. The disks protect the inner vessel and backup the relief valves in the event that the valves fail to operate properly. Unlike pressure relief valves, rupture disks, once activated, do not close. If they burst, the pressure and entire contents of the tank will be released.

Storage tanks are normally equipped with a pressure gauge that displays the internal pressure of the tank. Any abnormal conditions should be reported immediately. A differential pressure gauge may be used to measure the level of the liquid in the storage tank. The gauge translates the difference in pressure between the top and bottom of the tank into an estimated liquid level.

In some installations where liquid levels are critical to the operation, liquid-level sensing technology is used. A liquid-level signal is sent via cellular/internet-based telemetry systems or other means directly to the gas supplier, allowing the supplier to monitor end user gas use and to schedule gas deliveries based on demand. Gas deliveries should be carefully coordinated with the owner to ensure the appropriate resources are available to accept and release the gas prior to offloading from the truck.

Outer Vessel

An outer vessel is made of carbon steel or stainless steel. Under normal operating conditions, this vessel retains the insulation and vacuum around the inner pressure vessel. Typically, the outer vessel is not exposed to cryogenic temperatures.

The outer vessel of the storage tank is equipped with a vacuum breaker or vacuum rupture disk. This protects the outer vessel in the unlikely event that pressurized liquid or vapor leaks into the insulation space between the two vessels.

Insulation

The space between the inner and outer vessel contains several inches of insulating material maintained in a vacuum. The vacuum and insulating material help to reduce heat transfer and, thus, reduce the boil-off (also referred to as the NER) of the liquified gas stored within the vessel.

Vaporizing Systems

Most user applications use gases in their gaseous state. This is accommodated by converting the stored liquid to a gas using a vaporizing system. The vaporizing system may utilize ambient air or electric heating elements to ensure only gas is delivered to the POU. Vaporizing systems are usually equipped with a protective device (e.g., temperature sensor and interlock) downstream to prevent cryogenic liquid from reaching the customer supply line or process, which may not be designed to withstand the exposure to cryogenic temperatures. As the systems are often outdoor installations, the outer temperature may drop under the freezing point. Therefore, occasional electrical heating is used.

Frost or ice frequently builds up on the fins of the ambient air vaporizer system during gas use. The ice forms from the humidity present in the surrounding air. During periods of end-user shutdown or low gas use, the ice may melt or reduce in volume. In continuous gas use operations, ice may be present continuously on ambient vaporizers. Typically, icing should not exceed three-quarters of the vaporizer's length as excessive ice buildup can reduce the vaporizer's efficiency. Accordingly, it is recommended that any excessive ice buildup conditions are investigated as it may be an indication of excessive gas consumption (e.g., from a change in demand or leaks) or undersized evaporators.

Figure 4.3: Liquid Gas Storage Vessel and Vaporizing System

Image courtesy of Chart Industries, www.chartindustries.com.



Carbon Dioxide Storage Tank Installations

Carbon dioxide can be maintained in its liquid phase by one of two methods. The first method is storage in a vessel with increased insulation and a pressure control system with a higher-pressure rating (e.g., 350 psi (2413 kPa)) than other gases such as N_2 and O_2 . The second method is by storage in a vessel with an integral refrigeration system and pressure control system. Bulk carbon dioxide storage tanks are available in a variety of capacities, up to approximately 75 tons. Tanks are sized according to end-user demand and delivery requirements. Careful coordination during design phases is required for carbon dioxide systems as additional electrical requirements may be needed for the electric vaporizers when used.

Gas Distribution Piping Systems

Bulk gas piping systems are the responsibility of the owner once the gas supplier has installed the bulk storage tank, vaporizers, and pressure reduction station(s). The piping materials of construction must be appropriate for the gas contents and not negatively impact the quality of the gas. Typical materials of construction for pharmaceutical quality gases include copper tubing and stainless steel tubing. Where required (e.g., oxygen piping or ultra-high purity gases) piping systems that have been cleaned for oxygen service are utilized. The pressure and temperature ratings must also be appropriate for the overall system design. Piping systems should be installed in accordance with local laws and regulations. Proper labeling of piping systems ensures that mix-ups do not occur. Gas distribution systems should be maintained to be leak-free and under positive gas pressure so as to prevent contamination by atmospheric air.

Guidelines for labeling and tagging include:

- All valves and instruments are tagged and included on Piping and Instrumentation Diagrams (P&ID)
- Piping must be properly labeled (e.g., ASME A13.1 [29], European Council Directive 92/58/EEC [30]) to include contents and direction of flow:
 - Labels at each POU

- Labels approximately every 20 feet
- Labels at each branch takeoff
- Labels on both sides of every wall
- Labels on both sides of every floor penetration
- Labels properly color coded to reflect contents of piping and hazard

Cryogenic Distribution Piping Systems

Cryogenic piping systems for distributing liquid contents of the bulk storage tanks (e.g., Liquid N₂ (LN₂)) are the responsibility of the owner, once the gas supplier has installed the bulk storage tank. The piping materials of construction must be appropriate for the contents and not negatively impact the quality of the materials inside the pipe.

Stainless steel tubing is the typical material of construction for the distribution of cryogenic (liquid) pharmaceutical quality gases. For short sections, super insulated piping may be utilized. However, for more complex systems, Vacuum-jacketed (Insulated) Piping (VIP) systems are required. These super insulated and vacuum-jacketed piping systems are custom designed and very expensive to install; thus, care must be used to ensure proper design and installation. The pressure and temperature ratings are monitored and alarmed. Piping systems should be installed in accordance with local laws and regulations. Proper labeling and tagging of piping systems ensures that mix-ups do not occur. Guidelines for labeling and tagging are the same as those listed previously.

Figure 4.4: Anatomy of Vacuum Insulated Pipe (VIP) Part 1

Image courtesy of Chart Industries, www.chartindustries.com.

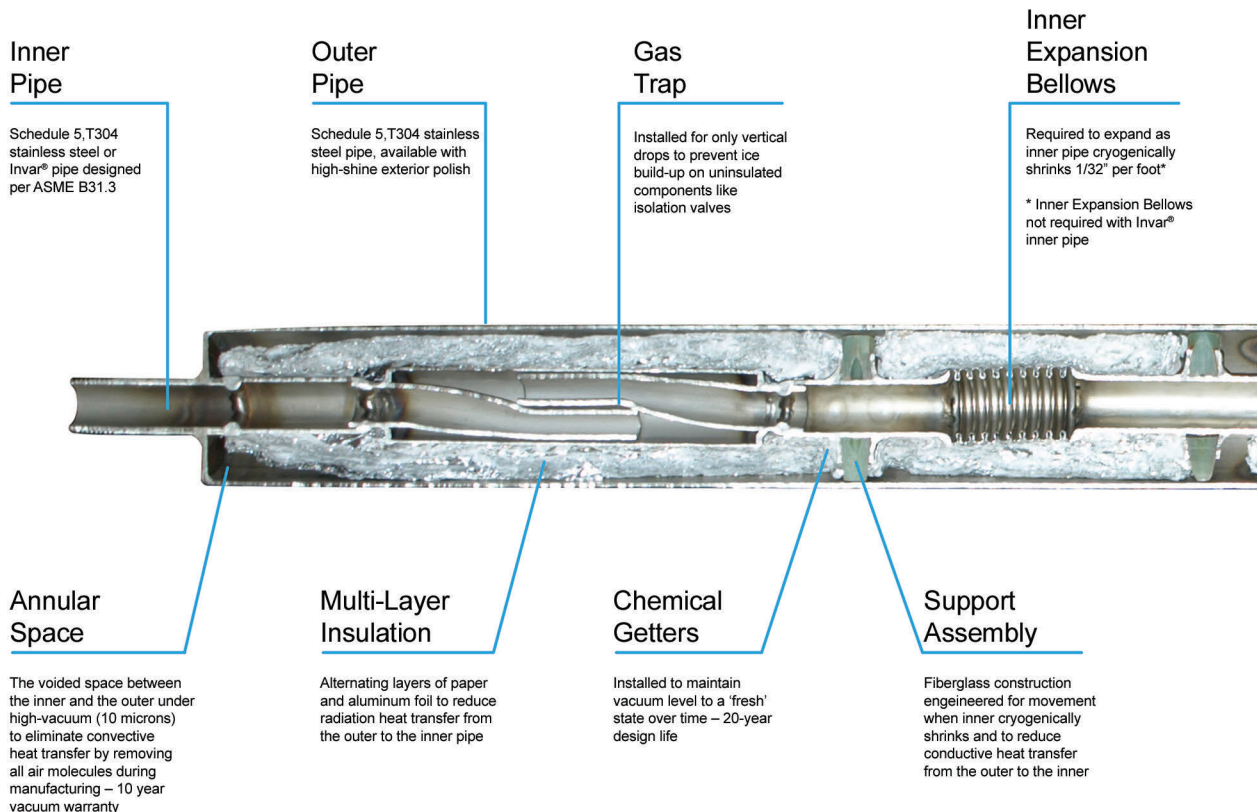
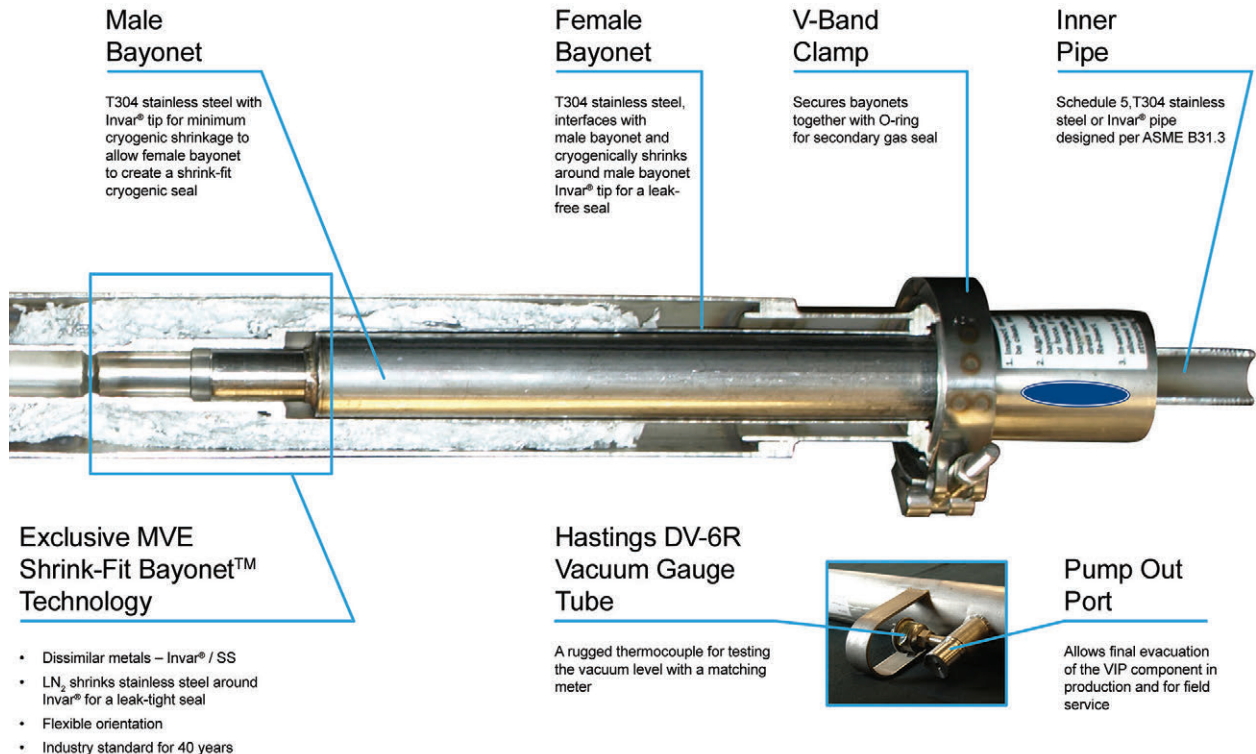


Figure 4.5: Anatomy of Vacuum Insulated Pipe (VIP) Part 2*Image courtesy of Chart Industries, www.chartindustries.com.*

Bulk Storage Tank Installation, Maintenance, Service, and Repair

Gas suppliers are responsible for bulk gas storage tanks and related controls and should install the necessary equipment in accordance with local laws and regulations as well as industry accepted standards and regulatory requirements.

A typical bulk gas installation system includes a structural concrete slab for mounting the tank, appropriate lighting and electrical receptacles, lightning protection, a fence with locking gate to prevent unauthorized access, proper signage indicating the hazards, and bollards or other methods to prevent damage from accidental vehicle collisions. For bulk oxygen systems, additional measures may be required for the delivery truck, such as a non-oxidizable unloading station to ensure any leaks do not come in contact with oxidizable substances such as asphalt. Additional physical segregation between other tanks or buildings may be required due to the oxidizing nature of the pure oxygen. These requirements are driven by local laws and regulations, gas supplier requirements, and company-specific safety requirements.

Customer responsibility normally begins downstream of the vaporizing system and/or at the outlet of the gas supply valve or regulator. Customers are also responsible for the downstream gas distribution system to the POU, including filtration and properly located and accessible sampling valves.

Only the gas supplier or authorized and trained personnel should maintain, repair, or adjust bulk storage tanks and related equipment and controls.

Any deficiency or system operating concern should immediately be reported to the gas or equipment supplier.