PHARMACUTICAL GASES

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PROPANE
UN 1978
NET WEIGHT
20 KG
OXYGEN
UN 1072
NET WEIGHT
20 KG
HELIUM
UN 1046
NET WEIGHT
20 KG
HYDROGEN
UN 1049
NET WEIGHT
20 KG
ARGON
UN 1006
NET WEIGHT
20 KG
NITROGEN
UN 1066
NET WEIGHT
20 KG
CARBON DIOXIDE
UN 1013
NET WEIGHT
20 KG
ACETYLENE
UN 1001
NET WEIGHT
20 KG

- Refrences:
- USP –NF
- BP
- EP
- PICs (Inspection of medicinal gases – Aide-memoire . Sep 2007)
- ISPE Guide Process Gases (ED2 – OCT 2023)
- WHO good manufacturing practices for medicinal gases (annex 5)
- EMA (Annex 15: Qualification and Validation Volume 4 – march 2015)

WHAT IS IT?

- Pharmaceutical Gases
- Medicinal Gases
- Process gases

- The gases that come into direct contact with the biopharmaceutical and pharmaceutical manufacturing process streams (ISPE)

WHICH?

- Compresses Air
- Nitrogen
- Oxygen
- Argon
- Carbon Dioxide
- Helium
- …

WHERE?

- **Gases that are commonly used in the pharmaceutical industry are:**
- Nitrogen for inerting or flushing
- Air for flushing
- Oxygen for fermentation
- Carbon dioxide for extraction and purification
- The quality of those gases is specified in the European and U.S. pharmacopeias.


N²

WHERE?

- Nitrogen

- used to protect precursors, reagents, and pharmaceutical products from reacting with oxygen
- as a packing gas in Ampule, blister packs and form-fill-seal (FFS) vials
- pressurizing agent to check for leaks in process equipment (such as tanks, vessels, and pipes).
- to discharge or transfer other fluids from storage tanks and reservoirs in a similar manner.
- in GC, as a carrier gas (ultra-high-quality)

OIL FREE COMPRESSED AIR

Air Compressor

WHERE?

- Compressed Air

- for flushing
- For pressurized air in mechanical systems. Pneumatic (compressed-air)
- For Drying

WHERE?

- **Oxygen:**
- **In sterile ampoule production**
- in fermenters using cell cultures. pure oxygen is used to “enrich” the internal environment, enhancing growth rates and productivity.
- In pharmaceutical synthesis (combination of roughly 10% oxygen with nitrogen)


IN
MA
TEC
O2
IN
MA
TEC
O2

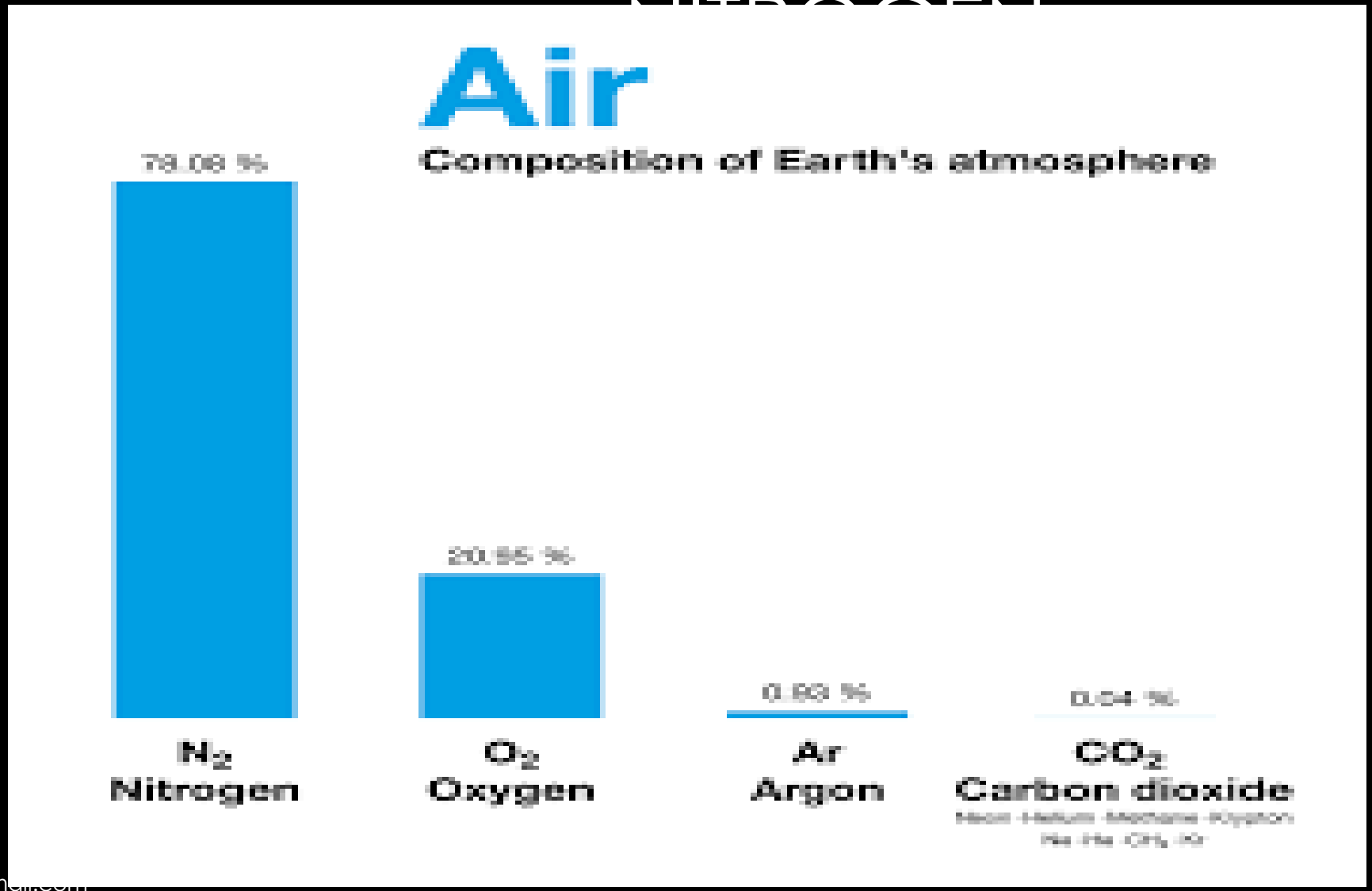
WHERE?

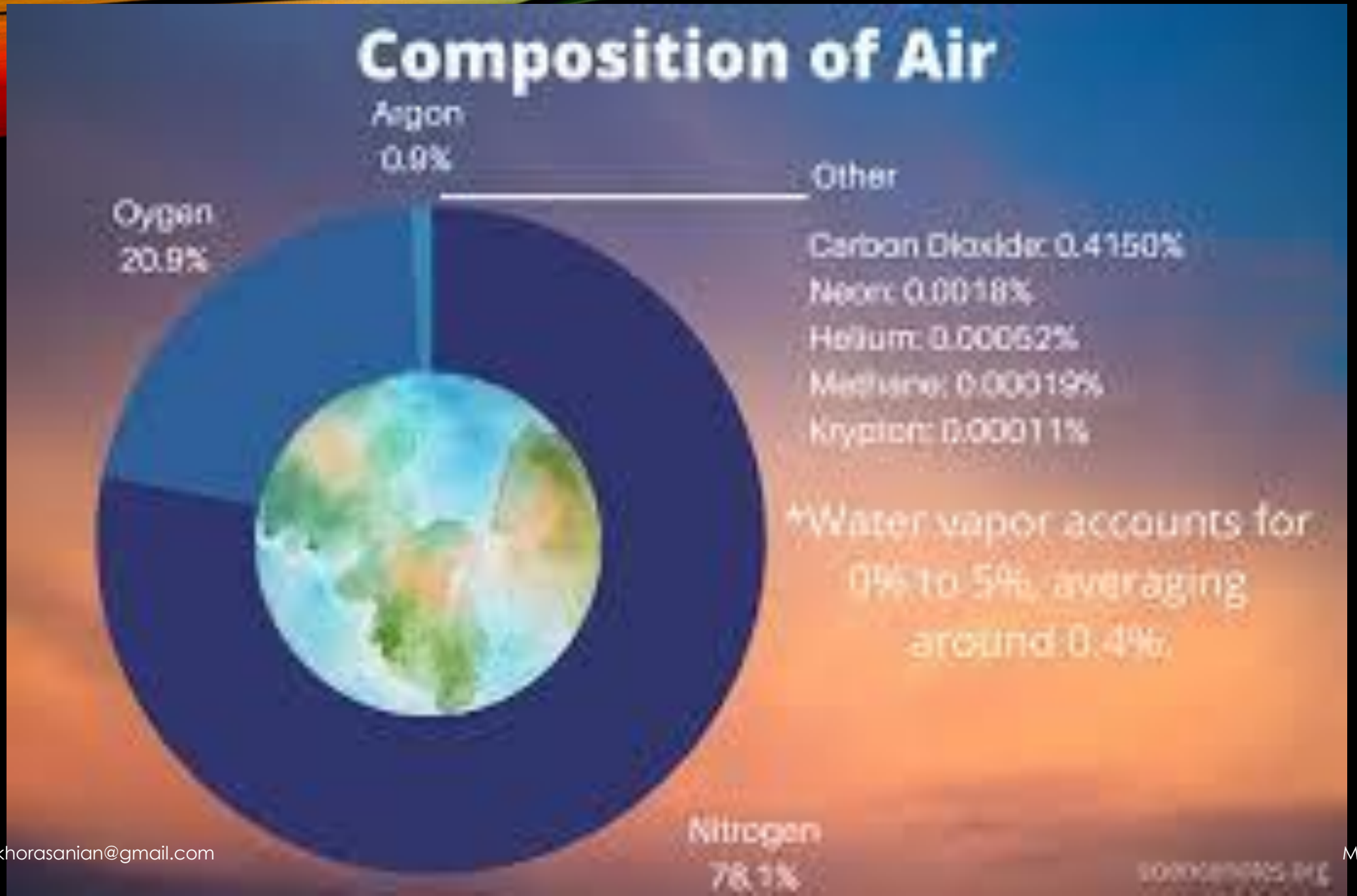
- **Carbon Dioxide**
- (CO_2) is inert, much like nitrogen
- ideal for general-purpose blanketing and packing.
- is employed as a supercritical fluid (an intermediate state between liquid and gas as high temperatures and low pressures.)
- for organic compound extraction
- for "micronization", the process of producing very tiny particles of active medicinal substances.


OXYGEN
MEDICAL OXYGEN


SOIL
COMPOSITION
45% Minerals
25% Air
25% Water
5%
Organic Matter

NITROGEN


Air
Composition of Earth's atmosphere
78.08 %
20.95 %
0.93 %
0.04 %
N_2
Nitrogen
O_2
Oxygen
Ar
Argon
CO_2
Carbon dioxide


Composition of Air
Argon
0.9%
Other
Oygen
20.9%
Carbon Dioxide: 0.4150%
Neon: 0.0018%
Helium: 0.00052%
Methane: 0.00019%
Krypton: 0.00011%
*Water vapor accounts for
0% to 5%, averaging
around 0.4%.
Nitrogen
78.1%

Gas	Element	Method	Specification
Air	O_2	EP 2.5.27 : Paramagnetic analyser	20,4% - 21,4%
	H_2O	EP 2.5.28 : Electrolytic hygrometer	max. 67 ppm
	Oil	EP 2.1.6 : Impaction	max. 0,1 mg/m³
	CO	EP 2.5.25 : Infra Red analyser	max. 5 ppm
	CO_2	EP 2.5.24 : Infra Red analyser	max. 500 ppm
	SO_2	UV Flurorescence analyser	max. 1 ppm
	NO/NO_2	EP 2.5.26 : Chemiluminescence analyser	max. 2 ppm
Nitrogen	N_2	EP 2.2.28 : GC-TCD with injection loop	min. 99,5%
	H_2O	EP 2.5.28 : Electrolytic hygrometer	max. 67 ppm
	CO	EP 2.5.25 : Infra Red analyser	max. 5 ppm
	CO_2	EP 2.5.24 : Infra Red analyser	max. 300 ppm
	O_2	Electrochemical analyser	max. 50 ppm
Oxygen	O_2	EP 2.5.27 : Paramagnetic analyser	min. 99,5%
	H_2O	EP 2.5.28 : Electrolytic hygrometer	max. 67 ppm
	CO	EP 2.5.25 : Infra Red analyser	max. 5 ppm
	CO_2	EP 2.5.24 : Infra Red analyser	max. 300 ppm
Carbon Dioxyde	CO_2	EP 2.5.24 : Infra Red analyser	min. 99,5%
	H_2O	EP 2.5.28 : Electrolytic hygrometer	max. 67 ppm
	CO	EP 2.2.28 : GC-FID with methaniser	max. 5 ppm
	S	UV Flurorescence after 1000°C oxydation	max. 1 ppm
	NO/NO_2	EP 2.5.26 : Chemiluminescence analyser	max. 2 ppm

CHALLENGES

- **testing of those gases is a real challenges for the industry :**
- Dedicated analytical equipment according to the pharmacopeias with the appropriate qualification
- Dedicated sampling method fully validated
- Trained and qualified technician with special focus on safety and security issues
- gas should also be tested in terms of particular contamination and bio contamination. The contamination of the gas should not be higher than the contamination of the room where it is used

EP

Nitrogen 99.5 %

NITROGEN, LOW-OXYGEN

Nitrogenium oxygenio depletum

which is used for inerting finished medicinal products which are particularly sensitive to degradation by oxygen.

Oxygen: maximum 5 ppm V/V,

EP

- NITROGEN 99.5%
- is monograph applies to nitrogen for medicinal use.
- **Oxygen.** Not more than 50 ppm V/V,
- **Carbon dioxide**: Not more than 300 ppm V/V,
- **Carbon monoxide**. Not more than 5 ppm V/V,
- **Water.** Not more than 67 ppm V/V
- **Assay : GC**

USP - NF

Nitrogen 99.0 %

- Nitrogen contains not less than 99.0 percent, by volume, of N2

Identification— Prepare a gas chromatograph…

- **Odor:** no appreciable odor is discernible.
- **Carbon monoxide:** not more than 0.001%.

Limit of oxygen— Not more than 1.0% of oxygen

Assay : GC

USP - NF

- Nitrogen 97 Percent
- is Nitrogen produced from air by physical separation methods.
- Assay: GC

Odor

- **Carbon dioxide:** not more than 0.03%.
- **Carbon monoxide:** not more than 0.001%.
- **Limit of nitric oxide and nitrogen dioxide:** not more than 2.5 ppm

USP -NF

Medical Air

is a natural or synthetic mixture of gases consisting largely of nitrogen and oxygen.

It contains not less than 19.5 percent and not more than 23.5 percent, by volume, of O2

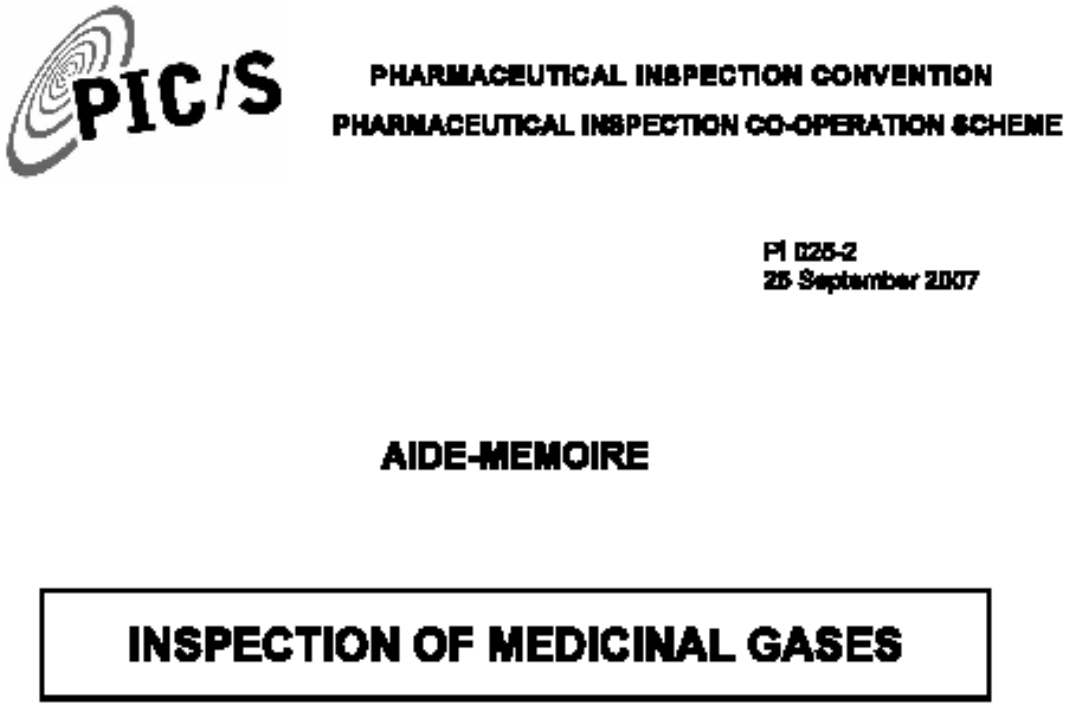
USP -NF

- Oxygen
- contains not less than 99.0 percent, by volume, of O2.
- [NOTE—Oxygen that is produced by theair-liquefaction process is exempt from the requirements of the tests for *Carbon dioxide* and *Carbonmonoxide*

USP -NF

- Helium
- contains not less than 99.0 percent, by volume, of He.

PICS



PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 025-2
25 September 2007

AIDE-MEMOIRE

INSPECTION OF MEDICINAL GASES

PICS

- Manufacturing of
- medicinal gases
- is regulated by the PIC/S GMP Guide and Annex 6

•- Air compressors

- - Maintenance frequency
- - Change and consumption of oil
- - Oil type used
- - Check of bearings
- - Air Cooled
- - Water cooled (water quality)
- - Pressure

- Crucial questions
- Type of compressor and oil used?
- If water could come in contact with medicinal gas: microbiology?

•Filters & /Molecular Sieves

- - Types
- - Changing frequencies
- - Proper installation
- - For sieves regeneration
- - Pressure drop
- - Integrity testing

- - What type of filters do they use?
- - SOP for maintenance?
- - How is (or is) really integrity tested for these filters?

•- Storage tank

- - Design
- - Maintenance
- - Tank pressure
- - Filling leve

•Quality control labs

- Test method
- Trend analysis
- Validation of analytical methods

Tubing distance for sampling and purging principles when performing analysis

Calibration gases

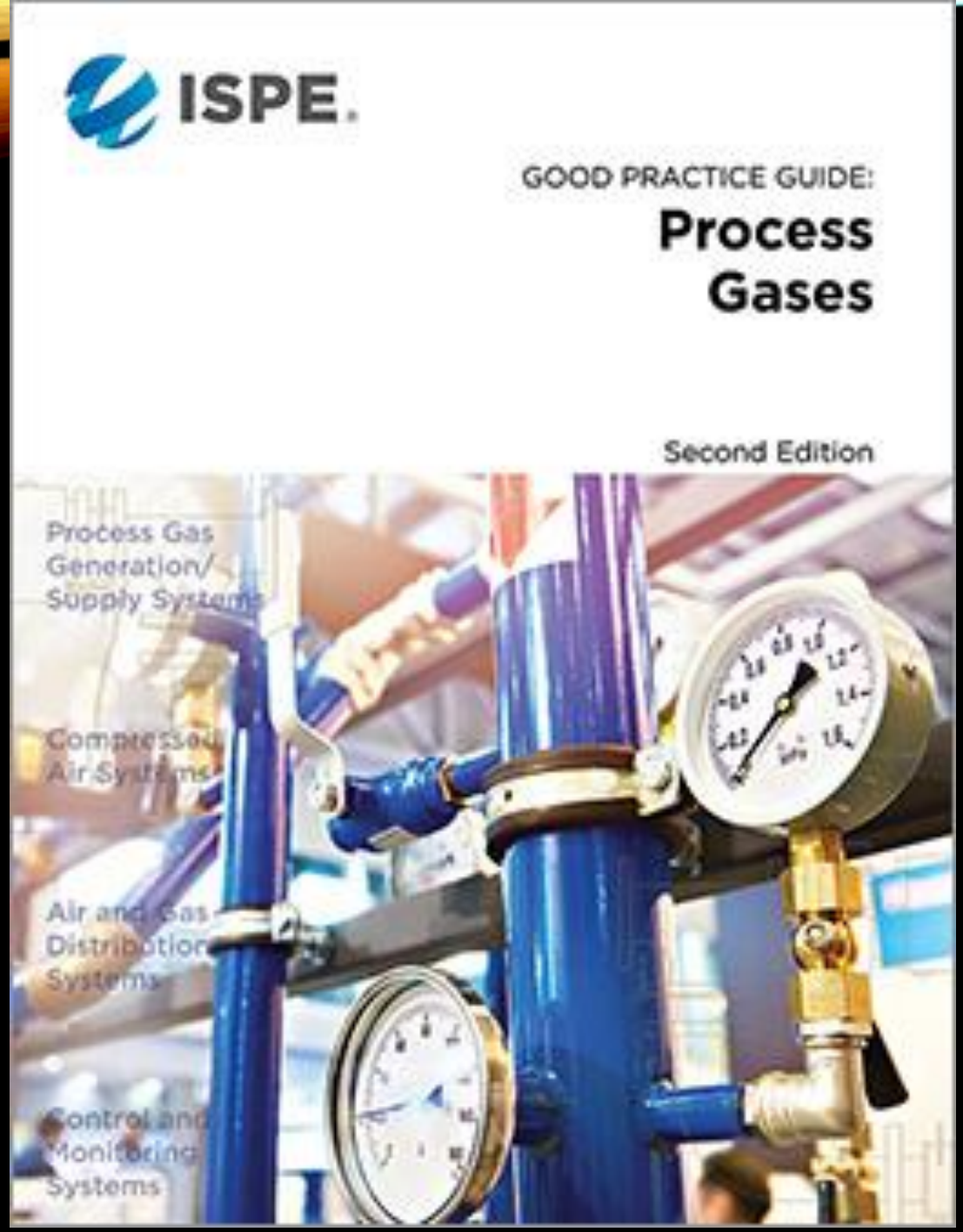
Standards

Microbiological contamination

Particles

OOS

- Cylinders
- Receiving and preparation
- Maintenance
- Storage
- Specification for cylinders and valves


ISPE.
GOOD PRACTICE GUIDE:
Process Gases
Second Edition
Process Gas Generation/ Supply Systems
Compressed Air Systems
Air and Gas Distribution Systems
Control and Monitoring Systems

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ISPE

- **2 Pharmaceutical Gases:**
- **Regulatory Requirements and Industry Best Practices……**

- GMP Requirements
- Gases Used for Pharmaceutical Production

Table 3.1: General Properties and Characteristics

Chemical Name	Nitrogen	Oxygen	Argon	Carbon Dioxide	Air, Compressed
Chemical Formula	N_2	O_2	Ar	CO_2	Mixture of N_2 and O_2
Appearance/Color	Colorless gas	Colorless gas Bluish liquid	Colorless gas	Colorless gas	Colorless gas
Odor	None	None	No odor warning properties	No odor warning properties	None
Molecular Weight (g/mol)	28.01	32.00	39.95	44.01	29
Boiling Point °F (°C)	-320.4 (-195.8)	-297.3 (-183.0)	-302.5 (-185.9)	Not applicable	O_2: -297.3 (-183.0) N_2: -320.4 (-195.8)
Sublimation Point °F (°C)	Not applicable	Not applicable	Not applicable	-109.3 (-78.5)	Not applicable
Critical Temperature °F (°C)	-232.7 (-147.1)	-181.4 (-118.6)	-188.1 (-122.3)	87.9 (31.0)	O_2: -181.4 (-118.6) N_2: -232.7 (-147.1)
Relative Density, Gas (air=1)	0.97	1.11	1.38	1.53	O_2: 1.11 N_2: 0.97
Solubility mg/l water	20	39	61	2000	O_2: 39 N_2: 20

Table 3.2: Typical Purity of Air Gases

	Typical Cryogenic Purity (min %)	USP/NF (min %)	EP (min %)	JP (min %)
Oxygen	99.5	99.0	99.5	99.5
Nitrogen	99.998*	99.0	99.5	99.5
Argon	99.997	-	99.995	-
*Nitrogen purity includes rare gases				

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Air Treatment

Treating compressed air to remove contaminants such as dirt (viable and non-viable particulate), lubricant, and water, may use equipment such as:

- compressor aftercoolers
- filters
- separators
- dryers
- air receivers
- traps
- automatic drains

A variety of standards can be used to define air quality. A commonly recognized standard is ISO 8573-1:2010 (Reference 7, Appendix 8) which identifies three classes of contaminants:

1. particulate
2. water
3. oil/oil vapor

Table 4.1: ISO 8573-1:2010 Air Quality Class

Quality Class	Particulate Max number of particles per m^3			Water Pressure Dewpoint (at) atmospheric pressure)		Oil and Oil Vapor
	0.1 – 0.5 micron	0.5 – 1.0 micron	1.0 – 5.0 micron	°F	°C	mg/m^3
0	As specified by the user or equipment manufacturer and more stringent than class 1.					
1	≤ 20,000	≤ 400	≤ 10	-100	-70	≤ 0.01
2	≤ 400,000	≤ 6,000	≤ 100	-40	-40	≤ 0.1
3	-	≤ 90,000	≤ 1,000	-4	-20	≤ 1
4	-	-	≤ 10,000	37.4	3	≤ 5
5	-	-	≤ 100,000	44.6	7	> 5
6	-	-	-	50	10	> 5

DRYER

Table 4.2: Comparison of Dryer Technologies

Technology	Initial Cost	Purge Air	Energy Cost	Dewpoints
Heatless	🟢	15%	🔴	-40°F to -100°F
Externally Heated	🟡	7 to 8%	🟡🔴	-40°F to -100°F
Blower Purge	🟡	0 to 3%	🟡🔴	-40°F
Heat of Compression – Drum	🔴	0%	🟢	0 to -20°F
Heat of Compression – Twin Tower	🔴	0 to 2%	🟢	< -20°F

FILTERS

Compressed Air Filters

Compressed air filters downstream of the air compressor are normally required for the removal of contaminants. Filters should meet criteria defined in the User Requirements. Types of filter available include:

- particulate filters to remove solid particles
- coalescing filters to remove hydrocarbon droplets, moisture droplets, and particulates
- adsorbent filters to remove hydrocarbon vapors and other aromatics (odors and tastes)

FILTERS

Figure 4.9: Sterilizing Filter Cartridges

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FILTERS

A particulate filter may be recommended after a desiccant-type dryer to remove desiccant dust. A coalescing-type filter may be recommended before a desiccant-type dryer to prevent fouling of the desiccant bed if a lubricant injected compressor is used upstream, or the local air quality may provide a risk of hydrocarbon in the compressor discharge. Filter grades of 0.45 µm or 0.2 µm may be employed at POUs.

When reviewing filters for their applicability, particle size removal ratings (e.g., 0.2 µm) and the filter efficiency rating (e.g., 99.97% efficient) should be reviewed. These ratings are normally based on defined inlet conditions, usually 70°F (21°C) at 100 psig. If the inlet conditions vary from those specified, the filter manufacturer should provide advice regarding the performance data based on the actual system conditions.

FILTERS

A typical sequence of filters for a system is:

1. **Particulate Filter:** typically 1 µm to 3 µm for removing rust, pipe scale, metal oxides, and desiccant particles

2. **High Temperature Particulate Filter:** Temperature spikes can occur when using a heated desiccant dryer. When the regenerated tower comes back online, heat generated during regeneration is picked up by the compressed air. Similar ratings to standard particulates apply, but can withstand the higher operating temperatures to 350°F to 450°F (176.7°C to 232.2°C).

3. **Coalescing Filters:** Coalescing filters are rated for particle and liquid aerosol droplet removal. Liquid droplet removal capacity is typically 0.001 ppm by weight and aerosol size rated at 0.01 µm.

4. **Final Filter:** A 0.2 µm liquid rated cartridge filter (down to 0.003 µm absolute rated for particles in gases) may be used as a final filter to obtain “sterile grade” compressed air. These filter cartridges are typically sanitary style to minimize the risk of bypass and incorporate a hydrophobic non-volatile membrane as the filter media.

TRAPS / DRAINS

Traps and Drains

Traps or drains allow the removal of condensate from the compressed air system to protect the equipment being supplied by the system from the effects of a non compressible fluid. Automatic condensate traps are used to conserve energy by preventing the loss of air through open petcocks and valves.

Methods to drain condensate include:

1. mechanical traps
2. solenoid actuated drain valves
3. zero air-loss traps with reservoirs
4. manual

CONTROL

Control Systems

There are three categories of system which are controlled:

- Compressed Air Systems
- Cylinder Systems
- On Site Gas Generation and Bulk Storage Systems

Compressed Air Systems

The compressors normally have a specific proprietary control system. This should control and monitor the compressor, shutting it down in the event of an alarm or sensor failure in order to protect the equipment. Usually compressor control is based on maintaining a minimum pressure at its discharge – on a basic system through shutting down or starting up the compressor, on a more sophisticated system through regulating the compressor output.

There is usually provision for interconnecting these control systems or linking them through a "supervisory" controller that will manage multiple compressors, usually rotating the primary duty unit to ensure equal use of each system.

The dryers within a system typically come with a supplier's proprietary control system. The control systems typically operate based on a timer to control the sequence of operation between the two dryer vessels or the changeover between vessels is controlled by the discharge pressure dewpoint. The latter system is considered more energy efficient.

In the event of a system failure, the alarm from a dryer pressure dewpoint monitor may be used to automatically close the valve downstream of the dryer, as this would prevent putting potentially wet air into a distribution system – where a sudden loss of supply would create problems, this signal could also initiate a standby dryer.

The system status and any system alarms can be fed through a Building Management System (BMS) to facilitate

Cylinder Systems

There are two basic types of cylinder systems:

1. Manual Changeover

2. Automatic Changeover

Manual Changeover

These require the standby cylinder to be manually selected when the duty cylinder runs on low pressure.

These basic systems do not provide capability for remote monitoring, though a low cylinder pressure switch may be provided for connection to either a local alarm, an alarm in the area in which the gas is used, or to a BMS.

Automatic Changeover

The system automatically changes over from a duty to a standby cylinder, and will give an alarm signal to notify the system owner that the empty cylinder needs to be changed. This may be connected to a local alarm, an alarm in the area in which the gas is used, or to a BMS.

On Site Generation Systems and Bulk Storage Systems

These systems are typically supplied and maintained by a specialist supplier; with their own control and monitoring systems.

The design and operation of these systems should be understood by the user, and alarm signals from the system made available for connection to a monitoring system, as required. Users may duplicate monitoring instruments for connection to their monitoring system to allow the gas system supplier to provide a standard package. This also has the advantage that the user retains management of the calibration of the devices.

The integration and monitoring of process gas systems should be considered during the design phase to ensure that the optimum solution is specified.

Where there are defined Lower Explosive Limits (LELs) for gas concentrations, monitoring systems and local safety alarms may be required by local regulations.

Monitoring

Operation Parameter Monitoring

Pressure is often categorized as a CPP for a process gas system, usually introducing a concomitant calibration and monitoring regime.

The gas supply system may be controlled by the pressure, either in the system receiver or in the entry point to the distribution system.

The distribution system should be sized so that end users receive the necessary flow and associated inlet pressure, based on design usage diversity or calculated pressure drop under peak usage.

This Guide proposes that the pressure is usually an engineering parameter and not a CPP.

The basis for this is:

- Any piece of equipment supplied by the gas system that has a requirement for a specific flow/pressure will have an inlet pressure switch that monitors and alarms for that use; this is a critical location/instrument.

- The system pressure control provides a general indication, but does not monitor at each POU, or consider any usage, or effect at an individual POU.

It may be appropriate to review specific installations to determine if that rationale is appropriate.

QUALITY MONITORING

Quality Monitoring

Quality monitoring is required at POUs located in controlled room environments. Regulations require that the particulate and microbiological quality of the compressed gas be equal to or better than that of the air in the environment into which the gas is introduced (at rest). (See Eudralex Volume 4 Annex-1, 2004; 21 CFR Part 210 (References 6 and 4, Appendix 8).)

Process gas systems may be operated at very low dewpoints or negative dewpoints, in accordance with user requirements. A properly operated process gas system with low moisture should not support the growth or survival o microorganisms.

WATER MONITORING

The quantity of water necessary to support microbiological growth is usually expressed as water activity (a_w). (It is used as a measure for the dryness of foodstuffs; therefore, the resistance to microbiological growth.) The use of water activity may be applied to non-sterile pharmaceutical products. (See USP/NF 31, General Chapter 1112 (Reference 14, Appendix 8).)

For gases, water activity is related to relative humidity (RH = a_w × 100%) and also dewpoint which may be used to express moisture in a compressed gas. Molds and yeasts do not grow where the a_w is less than 0.6 and bacteria do not grow where the a_w is less than 0.85 (Scott et al., 2001) (Reference 32, Appendix 8).

STERIL / NON STERIL

Process gas systems are not normally designed to be sterilized. Sterilization may apply to sections of a system, following the final filter, which are used for sterile applications. Typically these sections are outside the process gas system boundary and are part of the connected manufacturing system used for the sterile application. Control of microorganisms is usually accomplished at the POUs by using 0.2 µm sterilizing grade filters.

Inclusion of 0.2 µm sterilizing grade filters at a POU can ensure that process gas quality at a POU is equal to or better than that of the air in the environment into which the gas is introduced. Implementing a point in the distribution system that provides a break between non-GMP and GMP use during the design phase may provide an appropriate alternative solution.

The particulate and microbial levels present within the distribution system pre-filtration may be increased compared to the room environment if filter integrity can be demonstrated and levels do not exceed the certified filter retention rate.

For non-sterile applications, a filter pore size rating of 0.45 1 µm or 1.2 µm may be sufficient.

MICROBIAL TEST

Microbial Monitoring

Methods existing for monitoring environments (Downes and Ito, 2001 (Reference 28, Appendix 8)) may be extended to monitor process gases. The recovery medium for the microorganisms should include the growth media used in the environmental monitoring program for room air, surfaces, and personnel (PDA Technical Report No. 13 (Reference 24, Appendix 8)), as a minimum. The medium should include the demonstrated ability to support the growth of a variety of bacteria and fungi. Considerations should be made for additional growth media depending on the scope of the monitoring program. The sample device should be sanitizable or sterilizable prior to collection of each microbiological sample. Validation or performance qualification of the method should be considered prior to implementation. Such data may be supplied by equipment manufacturers and guidance may be found in ISO-14698-1, Annex-B (Reference 7, Appendix 8).

MICROBIAL TEST

Impaction

Slit to Agar Sampler

This method uses a revolving agar plate located at a specified distance from a slit orifice to impinge the sample air flow onto an agar surface. This device can sample a large volume of gas and can provide a time versus concentration relationship. The equipment is large, requires 150 mm agar plates, and is difficult to sanitize.

Impact Sampler

There are several impact type samplers available. This type of device pulls a stream of air through a metal plate containing many small and evenly spaced holes. The correct volume of air is directed through the holes and onto an agar surface.

The versions of these samplers for process gases are relatively large and difficult to sanitize. The attachments for monitoring compressed gases are large and bulky; however, the entire sample flow path and impaction plate can be steam sterilized.

These units have the advantage of sampling a cubic meter of gas in less than ten minutes.

Centrifugal Sampler

These samplers use a fan to pull a cylinder shaped cone of air into the sample head and particles or microorganisms are deposited by centrifugal force onto an agar strip within the sampling head. The sample head can be steam sterilized and the units are light in weight. Special agar stripes are required. Special adapters for sampling process gases are available.

Filtration

Filtration is a simple to use and low cost method for monitoring microorganisms in process gases, relative to methods requiring instrumentation. When numerous sample points should be monitored on a regular basis, it may be less costly to stock multiple filter holders than multiple sample instruments and sample heads/adapters.

The method consists of a type of filter holder (plastic or stainless steel), sterile filters, and a calibrated flow meter. The appropriate volume of gas is filtered through the filter and the filter is aseptically transferred to an agar medium for growth and enumeration. The membrane usually has a nominal pore size rating of 0.45 µm.

Membrane Filter

PARTICULATE M.

Particulate Monitoring

Instrumentation

There are several methods and a variety of instrumentation available for detecting, sizing, and quantifying particulates in compressed gases.

Methods include laser particle counting, condensation nucleus counting coupled with scanning mobility particle sizing, differential mobility analysis, and membrane capture. The application of these methods is covered in ISO-8573-4:2001 (Reference 7, Appendix 8).

The laser particle counter method is commonly used for process gases, due to the moderate sample rate, relatively low cost, and low maintenance requirements. Care should be taken to avoid including moisture as droplets in particle counts and to ensure that the sample hose connecting the particle counter and the sample point does not contribute to the particle count. The tubing should be made of a smooth non-shedding material and as short as possible to avoid particle fallout. The connection to the sample port should avoid introducing exterior air or generation of particles. Quick type connections should not continuously generate particles or allow introduction of exterior air through the venturi effect.

MOISTURE M.

Moisture Monitoring

Moisture in process gases is usually measured as dewpoint or pressure dewpoint. Methods usually include condensation devices, e.g.:

- cooled mirror dewpoint hygrometers
- electrolytic hygrometers
- impedance hygrometers
- polymer film relative humidity sensors

HYDROCARBONS M.

Hydrocarbons Monitoring

Compressed air and other process gas systems intended for pharmaceutical applications should be designed and constructed with oil free compressors and hygienic piping. The installation of systems should include the concept of "build clean" where the equipment and piping are supplied in a clean condition and installed in a manner to prevent contamination.

The monitoring of hydrocarbons in compressed gas systems contributes to the qualification phase to ensure the piping is free of oils prior to use. When compressed air systems are appropriately designed and installed, the most significant risk to the system is the introduction of diesel (auto) fumes at the air intake for the compressor. Air intake for compressors should be considered in the design stage and care should be taken to avoid introduction of fumes into the system.

Depending on the air quality in the vicinity of a facility, compressed air quality may need to be monitored on an ongoing basis for high risk contaminants. For contaminants presenting a hazard, which concentration is relevant and how often monitoring should occur should be considered.

Two distinct methods may be identified based on the type of hydrocarbon component targeted:

1. Total Hydrocarbon (THC)

2. Total Volatile Hydrocarbons (TVHCs)

HYDROCARBONS M.

Total Hydrocarbon (THC)

Total Hydrocarbon (oil mist) is the term for oils that can form an aerosol that will remain suspended in the air until it impinges against a surface. These may be detected and quantified using indicator tubes. The tubes contain chemicals that are designed to react with an introduced substance and changes color as a result. These are typically single use only. Oil indicator tubes are designed to monitor for specific oils and mists derived from a variety of mineral and synthetic oils. The detection limits are dependent on the volume of gas exposed to the tube medium and the specific type of oil. These tubes are not designed to detect hydrocarbon fumes.

Total Volatile Hydrocarbons (TVHCs)

Volatile hydrocarbons are compounds that are either gases or liquids that can evaporate and act as a gas. The method does not detect oil mists. TVHCs may comprise many different types of volatile hydrocarbons; therefore, are measured and expressed as parts per million calculated as methane.

RISK ASSESMENT

1. Gas Purity	Applicable for inert gases such as Nitrogen, as per USP/EU Monograph
2. Moisture (Water Aerosols or Vapor)	Non-sterile or sterile applications – NMT 2.5 g/kg (-40°F (-40°C) dewpoint)
3. Hydrocarbons (Oil Content)	NMT 0.5 mg/m^3
4. Other Chemical impurities (Only as Applicable)	Based on the generation technology and/or USP/EU Monograph
5. Microbial Count (Non-sterile Applications)	Guideline limits to be established based on product bioburden limits. Typical level NMT 5 cfu/m3
6. Microbial Count (Sterile Applications)	As per viable particle requirements for Grade area where the product is exposed to the compressed gas (e.g., Grade A, Grade A/B, Grade B or Grade C)
7. Particle (Viable and Non-viable Count)	Typically equal to the at rest condition of the area served

QRM

Quality Risk Management for Process Gas Systems

The Quality Risk Management approach should be applied throughout the life cycle of a process gas system and is described within this Guide to support:

- development of the User Requirements
- development and review of the process gas system design
- determination of the scope of verification testing activities (commissioning, installation, functional, and performance testing)
- determination of the optimum scope and scale of a calibration program
- determination of appropriate preventive maintenance programs
- determination of the scope and frequency of routine monitoring programs
- to ensure assumptions made during the risk assessment were appropriate during system operation

QRM

Risk Identification/Hazard Severity

Risk identification involves the systematic use of data to identify hazards that could affect CPPs, CQAs, or critical aspects of a process gas system. Risk identification should consider likely, rather than rare events such as earthquakes. A pre-defined scale can be used to rank the severity of impact of identified hazards on a process gas system.

Potential risks to typical product CQAs from a compressed air system include:

- hydrocarbon (oil vapor and particulate) content
- increased moisture levels
- viable particulates
- non-viable particulates (other than hydrocarbon)
- gaseous impurities
- process gas mix-up (e.g., connection of oxygen container to nitrogen distribution system)
- reverse flow

VALIDATION AND QUALIFICATION

- URS : User Requirements Specification
- System Risk Assessment
- DR & DQ : Design Review and Design Qualification
- Factory acceptance testing (FAT) /Site acceptance testing (SAT)
- IQ : Installation Qualification
- OQ : Operational qualification
- PQ : Performance qualification
- RE-Qualification