TECHNICAL BULLETIN

Prepared by WG-7 TB 44/22 – June 2022

Environmental Control and Monitoring for Medicinal Gas Cylinders

All medicinal gases and medicinal gas mixtures are stable products and do not have to be stored under controlled temperature conditions by the manufacturer to ensure that they are suitable for patient use when administered.
The only exception that is currently marketed is the 50% / 50% nitrous oxide /oxygen gas mixture, where the Healthcare Facilities are advised to store these immediately before use under the conditions specified in the Marketing Authorisation by the Marketing Authorisation Holder to ensure it is ready for use. Even if the cylinder is stored at low temperatures, where the nitrous oxide condenses out of this mixture, the mixture will return to its original specification, provided the cylinder is stored as instructed.
Regarding environmental humidity, all medicinal gases are stored at high pressure in cylinders and the gas is not exposed to the atmosphere whilst in storage. Hence there are no requirements to control the humidity when storing or transporting the gas cylinders.
Therefore, it can be summarised that for medicinal gases and gas mixtures there are no temperature and humidity controls required for the storage and transportation for high-pressure cylinders.

Introduction

When a gas is compressed and supplied in a high-pressure cylinder, it is considered as dangerous goods under the ADR regulations, which covers the transport of dangerous goods on the road. These regulations require the cylinders to be designed and constructed to the approved European /International standard covering the type of cylinder package which specify the temperature range to ensure the safety of the cylinder (and not the quality of the product they contain).
When the gas is intended for medicinal use, high pressure gas cylinders also need to comply with the basic requirements of the European Directive 2001/83/EC. This legislation covers the requirements for the manufacture and distribution of medicinal products and specifically, the way in which the products should be stored and handled prior to supplying to the healthcare facility or directly to the patient. These regulations require the temperature range to be specified to ensure the product is suitable for patient use.

This Technical Bulletin provides the rationale for the storage and handling requirements for medicinal gas cylinders, specifically to justify the reasons why it is not necessary to control the temperature or humidity of the areas where medicinal gas cylinders are stored, or the design of vehicles used for distribution.

ADR Regulations

Within Europe, the Agreement concerning the International Carriage of Dangerous Goods by Road (ADR) specifies the design, construction and testing requirements for high pressure gas cylinders transported on the road. These requirements apply to all high-pressure gas cylinders and cross reference the appropriate International (ISO), European (EN) or national standards that detail their design requirements.
Within these standards, the design requirements are based around a working pressure (normally defined at 15°C) for the cylinder and an appropriate design pressure, (based on 1.5 times the working pressure), that the cylinder should not exceed.
When the gas in a cylinder is heated (either by storage at elevated temperatures or exposure to heat), the pressure in the cylinder will increase, as defined by the Gas Laws. As you increase the temperature of any gas or gas

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mixture, the pressure will increase at a rate dependent on the specific gas and its actual pressure.
To ensure that cylinders do not exceed their design pressure, the relevant standards specify a maximum temperature of 65°C. The standards also specify a minimum temperature to which cylinders should not be exposed (-40°C), to ensure that the cylinder is safe to handle and will not fail if dropped.
The temperature range chosen by the ADR is based on climatic conditions recorded within Europe, ensuring that all cylinders manufactured in Europe can be used safely without any special conditions.
Table 1 specifies the developed pressure for medical oxygen in cylinders of different working pressures, demonstrating that they will always be within the design pressure limits.

Product	Working Pressure Bar(g) at 15°C	Developed Pressure at 65°C Bar(g)	Design Pressure Bar(g)
Medical Oxygen (99.5%)	137	170.4	205
	200	254.5	300
	230	295.4	345
	300	391.7	450

Table 1 Developed Pressures for Medicinal Oxygen

It is the responsibility of the gas supplier to inform their customers of the working temperature range for the storage and handling of the cylinders they supply. Under normal conditions, cylinders would not be exposed to temperatures outside this range, unless stored close to heating sources such as boilers and radiators.
As a consequence, suppliers of medicinal gases, supplied in high pressure cylinders have provided the ADR temperature ranges within the special storage conditions of the Summary of Product Characteristics (SmPC) for the medicinal products they supply.

Note: *The ADR temperature range is only concerned about the developed pressure of any gas when heated to 65°C and has no bearing on the stability of the medicinal gas.*

Pharmaceutical Regulations

The basic pharmaceutical regulations covering the control of the temperature and humidity of the storage conditions for medicinal products is covered by the Guidelines on Good Distribution Practice of medicinal products for human use (2013/C 343/01).
Section 6.4 of the GDP Guide specifies that active substances should be stored under the conditions specified by the manufacturer when necessary to ensure that the quality of the medicinal products do not deteriorate between the final product testing and the supply to the patient. These conditions can include the control of the temperature and humidity of the storage conditions.
With respect to the temperature control requirements for medicinal gases, the Marketing Authorisation Holder is required to specify any special storage conditions in the SPC. This information normally relates to the safety of the cylinder package and not the quality of the gas contained in the cylinder.
As the temperature range is well within the extremes experienced in Europe, there are no requirements to monitor storage (or transport) temperature conditions, provided the storage arrangements are located away for sources of heat.
With respect to the need to control the humidity of the storage arrangements, Annex 6 of the European GMP Guide indicates that the manufacture of medicinal gases is generally carried out in closed equipment, and as a consequence, environmental contamination of the product is minimal. This statement is strengthened where the valves fitted to the high-pressure cylinders are fitted with residual pressure devices, which maintains the cylinder at a minimum pressure after use to prevent the contamination of the cylinder. Hence the environmental humidity conditions, for storage and distribution, have no impact on the quality of the gas and does not require to be controlled.
Provided cylinders are supplied in a condition that is suitable for patient use, the GMP Guide indicates that there are no specific storage requirements for medicinal gas cylinders. Providing the gas outlets used for administration to the patient are protected by a cover, filled cylinders may be stored outside and not under cover. Where they are stored within a building, the storage area must not be adjacent to boiler rooms or any other facility where the temperature exceeds 65°C.

Medicinal Gas Mixtures

Medicinal gas mixtures follow the same Gas Laws as single gases. The one exception to storage requirements for medicinal gas cylinders is where gas mixtures contain a proportion of a liquefied gas, where cold temperatures could cause this component to condense out of the gas mixture, which could change the quality of the gas administered to the patient. As the reduction on pressure is a consequence of the partial pressure of the liquefied gas component of the mixture, this effect would only be seen where the proportions of the liquefied gas are above 20% [1].
The 50%/50% mixture of oxygen and nitrous oxide is currently the only licensed gas mixture which could be affected by this phenomenon. Where the temperature of the mixed gas falls below approximately -5°C, there is a risk that the nitrous oxide will condense out of the gas phase and remain as a liquid in the bottom of the cylinder until either the pressure reduced or the temperature increases, causing the nitrous oxide to boil and return to the gas phase. The consequences of this are that the gas administered to the patient will be oxygen rich to begin with and then nitrous oxide rich as the cylinder is emptied.
The attached liquid/vapour phase diagram indicates the effect of temperature and pressure on the nitrous oxide / oxygen gas mixture homogeneity. Variation in the pressure with temperature for the gas mixture will have an effect on when the Nitrous oxide will condense out of the gas mixture.

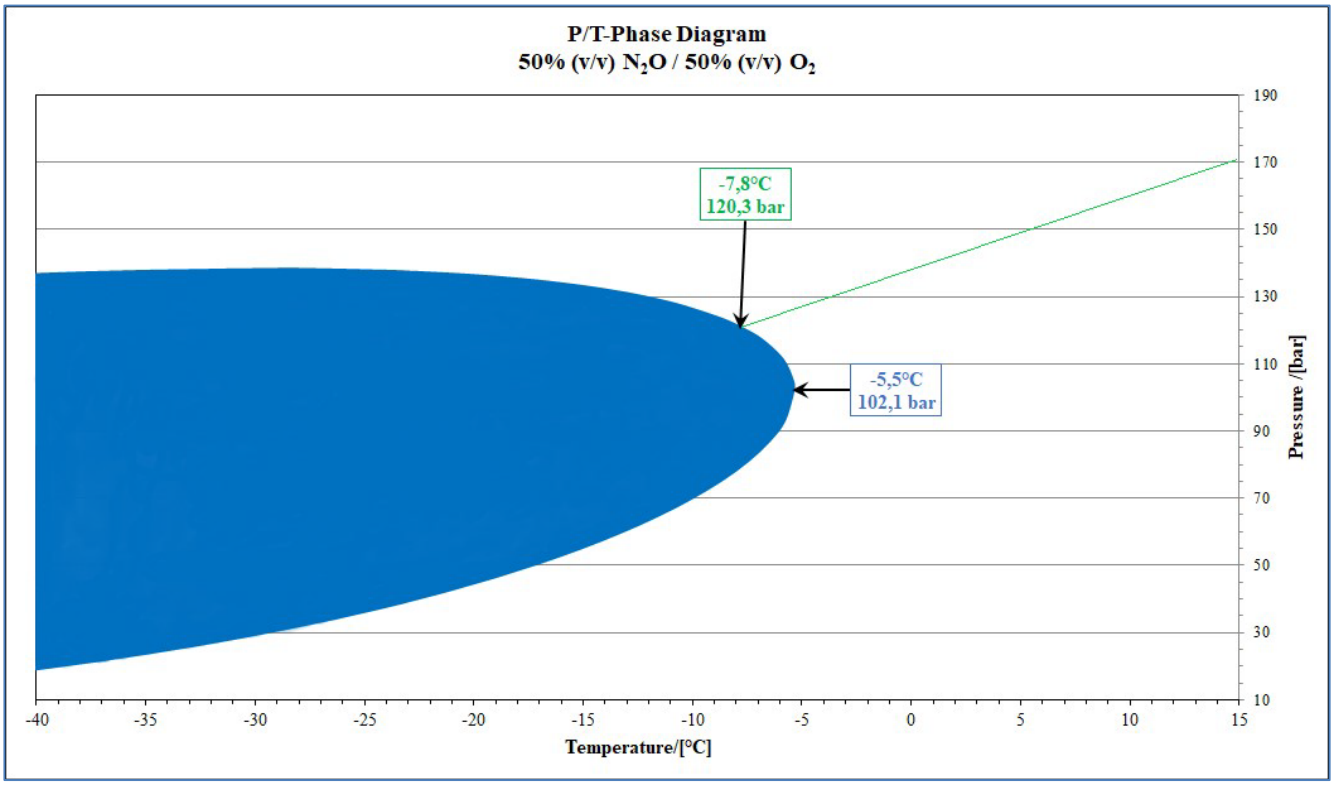

Fig. 1 Effect of temperature and pressure on nitrous oxide-oxygen homogeneity (modified from [1])

***Note**: Only to the left of the area of the curve (blue part in the figure) will condensation occur. If the gas temperature is to the right of the curve, the nitrous oxide will remain in the gas phase and no condensation will occur.*
Once the temperature of the mixture reaches the curve, condensation of nitrous oxide could begin, and the mixture could lose homogeneity. For example, for a cylinder filled to 170bar at 15°C, as the temperature is reduced the pressure will drop slightly, following the green line in the figure, but the mixture will remain homogeneous. When the temperature reaches the vapour saturation curve at approximately -7.8°C (at 120.3 bar) liquid nitrous oxide could be formed. The figure demonstrates that the maximum temperature at which phase separation could occur and result in formation of nitrous oxide in the liquid phase is approximately at -5.5°C, corresponding to a pressure of 102 bar.

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Validation studies have been conducted to demonstrate that, if separation has occurred due to low temperature, once the cylinder contents are warmed to above -5°C, the nitrous oxide will start to return to the gas phase without the need for any additional mixing requirements.
As a consequence, the accepted controls about the storage of 50%/50% mixtures of oxygen and nitrous oxide is that they should be stored horizontally at above 5°C for at least 24 hours before use [1]. These instructions are provided within the SmPC and PIL for the product and normally displayed on the cylinder label.

***Note**: There has been no cases where condensation of the nitrous oxide has been recorded with the use of this gas mixture (normally used as an analgesic in obstetrics and general pain relief) within Europe over the past 60 years.*

8 References

[1] Bracken AB, Broughton GB, Hill DW: *Equilibria for mixtures of oxygen with nitrous oxide and carbon dioxide and their relevance to the storage of N2O/O2 cylinders for use in analgesia.* J Phys D: Appl Phys 1970, 3:1747-1758.

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