TECHNICAL BULLETIN

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Microbiological Quality of Medical, Pharmaceutical and Food Grade Gases

1 Introduction

This Technical Bulletin details EIGA's position concerning the microbiological quality of gases used in medical, pharmaceutical and food applications. It is intended to assist in providing answers to both end users of the gases and to Regulatory Authorities questioned about the microbiological quality of gases.

There are no specific standard requirements for the levels of microbiological contamination within the specifications for food grade gases, but the European Pharmacopoeia specifies a general requirement for inhalation products in Chapter 5.1.4 Microbiological Quality of non-sterile pharmaceutical preparations.

Although the gases supplied for these purposes are not specified as being sterile, the adopted processes and procedures within the gas industry ensure that the manufacturing and filling process limit the microbiological contamination. All the testing carried out by the industry, has shown typical values of microbiological contamination significantly lower than the limit set by the European Pharmacopoeia.

The term medical in this document refers to both medicinal gases, used for administration to patients, and medical gases, used as a medical device, as specified under the European Medical Device Regulation 2017/745.

2 Scope

The scope of this document specifically covers the microbiological quality requirements for gases used for medical, pharmaceutical and food applications. It covers compressed and liquefied gases supplied in high pressure cylinders, and cryogenic liquids supplied by tankers into bulk storage tanks or in portable cryogenic containers.

It covers the quality of the gas up to the point of delivery into the customer's storage tank or at the outlet valve in high pressure cylinders or portable cryogenic containers. It does not address the quality of the gas once it has been distributed to the usage point via the customer's pipeline system. It does not cover medicinal or food grade gases that are produced using either Pressure Swing Adsorption (PSA) or Air compressing plants on the customer's premises.

This Technical Bulletin relates only to the microbiological quality of the gas and does not cover the external condition of the container.

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3 Conditions for minimizing contamination

The gases used for medical, pharmaceutical and food applications are manufactured and supplied from a number of different types of sources and processes.

Analysis studies, carried out by the gases industry, have shown that the levels of microbiological contamination of compressed, liquefied and cryogenic gases are well below the levels specified in the European Pharmacopoeia Chapter 5.1.4.

Contamination is minimized by manufacturing the gases in closed systems and supplying them under pressure, ensuring no contact with ambient air. In addition, they are maintained at extremely low moisture levels, making the conditions for microbiological growth unfavourable.
Where water comes in contact with the process gas, as part of the manufacturing process, the water quality is controlled (as defined in the EU Guidelines of Good Manufacturing Practices) using validated methods. Either drinking water quality or special treated water shall be used to ensure microbiological contamination is minimised.
As part of the manufacturing process, the gases are dried prior to the final process steps, which ensure that any microbiological growth in the gas is minimised.
For gases supplied in cylinders or cryogenic containers, the valve outlets are covered after filling to ensure no contamination enters the outlet. For cryogenic and liquefied gases supplied by tanker, the transfer hose is back purged with gas prior to making the delivery to ensure that any contamination with the hose is removed prior to the product being transferred to the customer tank. In addition, the extreme temperatures are not favourable for microbiological growth.
There have been no pharmacovigilance cases or food safety alert reported where microbiological contamination was involved.

4 State of the art - description and discussion

EIGA companies have performed testing for microbiological activity to verify that the microbiological level complies with the European Pharmacopeia acceptance criteria. These are summarized in a scientific report EIGA Doc 232/20 [1]. The scientific report mentions references for gas sampling and analysis methods. The main finding of the report is that gases have a very low or negligible microbiological content of bacteria and yeast (< 200 CFU/m^3) and they do not carry pathogens (absent in 1 m^3). This fulfils the requirements of the European Pharmacopeia chapter 5.1.4 Microbiological quality of non-sterile dosage form for inhalation (< 200 CFU/ml for TAMC - Total Aerobic Microbial Count - and < 20 CFU/ml for TYMC - Total Yeast Microbial Count -). The microbiological contamination in cylinders is of the same magnitude and well within these acceptance criteria.

5 Proposed Test Methods

As microbiological contamination of gases is well below set criteria there is no need for routine microbiological testing of gases.
Where there is a specific need to test the gas, it should be carried out by appropriate trained personnel familiar

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with the specific sampling requirements for gases under high pressure and cryogenic conditions.
The method of testing should be selected as reported in the scientific report. The sampling equipment including the pressure regulators have to be conditioned correctly to avoid cross contamination.
Currently, except for the bubbling method, all sampling methods give comparable results but only the impaction method is standardized in ISO 8573 part 7 Compressed air – test method for viable microbiological contaminant content.

6 Use of gases as finished products

Whereas the gases are supplied to the end user in a controlled condition, the end user should also carry out a risk assessment of their complete system to establish if there are risks associated with their distribution systems that could contaminate the gas. Where there is a requirement for the microbiological contamination of the gas to be controlled, appropriate bacterial or virus filters at the point of use should be used.
Maintenance regimes should be established to ensure that filters are changed at an appropriate frequency, as defined by the manufacturer of the filter or the user.

7 Conclusion

In gases there is an extremely low level of microbial counts and absence of pathogens. Moreover, the manufacturing and filling processes conditions (temperature, pressure, low level of humidity and nutrients) are extreme and the growth conditions are unfavourable when storing gases in tanks and gas packages. Ambient cross contamination is not possible because gas is always produced, stored and transported in closed systems and packages. Finally, at the gas usage point depressurisation during usage damage the microbial cells.

EIGA members apply a number of best practices in the treatment and handling of the gases to minimise the microbiological contamination These practices include the treatment of any process water that may come into contact with the gas and the quality of the water used to hydraulically test cylinders. Furthermore, the gas is kept in a dry condition, preventing microbiological growth.

EIGA members' tests have proven that gases used for medical, pharmaceutical and food applications are not vehicle to microbiological contamination.

Based on the above discussion, analytical measurement data confirm that the microbiological quality of gases are well below the European Pharmacopeia acceptance criteria for non-sterile products for inhalation use.
Based on the review of the above documents it is not required to monitor the quality of gases compared to the acceptance limits of the European Pharmacopoeia.

8 References

[1] EIGA Doc 232 *Microbiological Quality of Medical and Food Gases Review - Scientific Report* www.eiga.eu

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