QUALITY OF DELIVERED PRODUCT FROM MEDICINAL GAS CYLINDERS

AIGA 120/22

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Acknowledgement

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ABSTRACT

This publication has been originally prepared by the European Industrial Gases Association to present data that shows that metallic particles do not migrate from medicinal gas cylinders in quantities that could be considered toxicologically relevant.

Medicinal gases are authorised according to European Union Directive 2001/83/EC as medicinal products, this includes their container closure system, which in the case of gases consists of cylinders and valves.

No serious adverse reactions have been detected through the pharmacovigilance systems of the EIGA Member Companies arising from inhalation of particles migrating from the gas cylinder.

EIGA have conducted analytical tests in order to measure metallic elements, that could be present in medicinal gases. The results have concluded that impurities measurements are below the detectability levels as well as below ICH Q3D requirements.

EIGA (and also AIGA) are therefore of the opinion that the medicinal gases including their container closure systems do not present any risk to the patient by migration of metallic particles in toxicologically relevant quantities. Consequently, leaving the benefit-risk balance of medicinal gases unchanged. This publication explains in detail the tests conducted by EIGA Member Companies to confirm the physical view point of flows inside of gas cylinders.

1 Introduction

Since the late 1800s many millions of people have relied upon medicinal gases being supplied to them from gas cylinders. These gases are used for a wide range of procedures and modern healthcare systems could not survive without the safe delivery every day of medicinal gases, in particular medicinal oxygen from thousands of gas cylinders.

Medicinal gases supplied in high pressure gas cylinders have an excellent patient safety record and this publication demonstrates the intrinsic safety of the delivered package as well as the processes and procedures undertaken to ensure the safety of the delivered product. The publication considers a number of areas including how medicinal gases have evolved and how the gas cylinder package has developed into a technically advanced item of equipment. Section 7 describes a study conducted by EIGA Members on the delivered quality of medical oxygen. Section 6 indicates there is no evidence of safety concerns regarding patients receiving medicinal oxygen.

2 History of medicinal gases

The predominant medicinal gas used by patients is oxygen. This is almost exclusively produced in air separation plants, usually referred to as ASUs.

The earliest recorded use of oxygen in medicinal applications was at the end of the nineteenth century. Production of oxygen was not widespread and so the opportunity to obtain the gas was limited, though the benefits of using oxygen were immediately appreciated by medical practitioners. As production of oxygen for industrial processes developed, so did availability of oxygen for use in medical applications. The use was linked to the development of high pressure gas cylinders that could store sufficient quantities of the gas and be economic to transport. Several other technologies contributed to this increasing use of oxygen, such as the inventions of flexible tubing and the face mask.

The benefits of oxygen therapy became apparent during the first world war to treat the effects of poison gas. From 1918 onwards, the increased production of low cost oxygen ensured that oxygen therapy could be provided on a wide scale.

As the industrial gases industry has progressed to higher pressures, lighter cylinders and improved delivery systems, these benefits continue to be made available to the users of medicinal gases.

It should be noted that medicinal gases, including their packaging, are subject to the same authorization processes as other medicinal products, thus requiring the same modules for the container closure

system. In the case of medicinal gases these container closure systems are the cylinders and valves. The approval of the different types of cylinders and valves covered in this publication are therefore a significant part of the authorization process for medicinal gases.

3 Types of gas cylinder package

The package used to distribute compressed medicinal gases consists of primarily of two parts; the cylinder and the cylinder valve. To facilitate the safe delivery of compressed gases in cylinders, other accessories can be used such as regulators and flowmeters.

Examples of typical gas cylinder packages in common use are shown in Figures 1, 2 and 3.

Figure 1 Example of a cylinder valve and valve protection

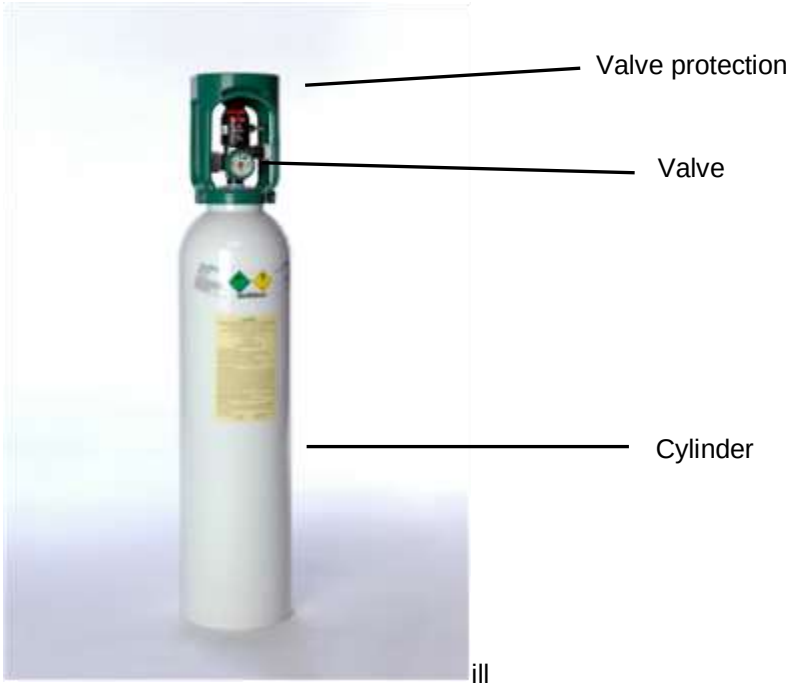

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Figure 2 Example of a gas cylinder package

Figure 3 Example of gas cylinder package with accessories

3.1 Gas cylinders

Today, most high pressure gas cylinders in medicinal gas service are of seamless steel construction, and are filled to a working pressure upto 200 bar.

These steel cylinders are constructed to European, International or local Standard , for example EN 1964, *Transportable gas cylinders. Specification for the design and construction of refillable transportable seamless steel gas cylinders of water capacities from 0,5 litre up to and including 150 litres. Cylinders made of seamless steel with an Rm value of less than 1100 MPa* and ISO 9809-1 *Gas cylinders -- Refillable seamless steel gas cylinders -- Design, construction and testing -- Part 1: Quenched and tempered steel cylinders with tensile strength less than 1 100 MPa,* [1,2][1]. These standards have undergone a rigorous development process by international standards organisations, such as CEN and ISO with participation by many EIGA members or Local standard, cylinder manufacturers and other stake holders. The steels used for the manufacture of gas cylinders are advanced alloys. Before these cylinders can be placed on the market within the European Union, they are subjected to rigorous approvals as required by legislation such as Directive 2010/35/EU - *on transportable pressure equipment* (TPED) [3].

In addition to steel gas cylinders there are also aluminium alloy gas cylinders in use developed and approved through a similar process as steel cylinders.

With technical advances, the suppliers of medicinal gases are increasingly looking to cylinders of a composite construction. These composite cylinders have a metal liner that is overwrapped with a fibre, such as carbon fibre.

3.2 Gas cylinder valves

The gas cylinder valve is the interface between the user and the delivered product and EIGA Members have expended considerable effort to ensure that this interface both satisfies all technical requirements as well as assisting the user in the delivery of the product. All valves are required by legislation to be type approved by competent authorities, based on requirements that include:

- ADR *European Agreement concerning the International Carriage of Dangerous Goods by Road* [4];

[1] References are shown by bracketed numbers and are listed in order of appearance in the reference section.

- *Transportable Pressure Equipment Directive* [1];
- EN ISO 10297, *Gas cylinders. Cylinder valves. Specification and type testing* [5];
- EN ISO 10524-3, *Pressure regulators for use with medical gases. Pressure regulators integrated with cylinder valves* [6];
- EN ISO 15996, *Gas cylinders. Residual pressure valves. General requirements and type testing* [7].

There are a number of different types of cylinder valves in use, and these are summarised below.

3.2.1 Standard gas cylinder valves

The basic gas cylinder valve is usually referred to as an O-ring valve. The name refers to the sealing mechanism which is an O ring located on the valve spindle that ensure leak tightness of the valve. There are many millions of these types of valves in service around the world and they are renowned for their reliability.

3.2.2 Residual pressure valves

In addition to the standard gas cylinder valve more and more residual pressure valves (RPV) are being put into service. Residual pressure valve can be with or without Non return function This type of valve adds an additional function to the standard valve by having a device that prevents impurities such as moisture and other contaminants entering the cylinder during use.

3.2.3 Valves with integrated pressure regulator (VIPR)

Beside the RPV, more sophisticated valves with an integrated pressure regulator (VIPR) are in use. This type of valve has not only a residual pressure function but delivers the medicinal oxygen at the required pressure and gas flow to the patient. VIPRs also prevent the backflow contamination.

4 Filling of gases into gas cylinders

Oxygen is produced from cryogenic distillation in air separation plants. These plants take atmospheric air and compress, purify and expand the air to liquefy it to cryogenic temperatures. Oxygen is then distilled from the liquid air. For medicinal gases produced in air separation plants there is a requirement for a manufacturing authorisation for the production process.

The cryogenic liquid product is distributed to a specialist cylinder filling facility where the product is filled into gas cylinders as a compressed gas.

The production/filling process of medicinal gases into cylinders have numerous controls and check points that include:

- Cylinder charging pressure is appropriate for the cylinder and valve combination;
- Cylinders and valves are within periodic inspection period;
- Confirmation that valves are suitable for the gas service;
- Verification there is a positive residual pressure inside the cylinders;
- Cylinder bodies, where appropriate, have been painted according to the applicable standards and guidelines; and
- Cylinders and valves are clean and not damaged;

Once the pre-filling inspection have been completed, the cylinders are connected to the filling system. Cylinders are usually filled in batches. During filling the valves are examined and verified to be free from leaks. At the end of filling new batch labels are attached to the cylinders.

Depending of the batch size one or more cylinders are analysed for the quality of the gas, to confirm that the batch is in accordance with the specifications in the monographs in the Local Pharmacopeia.

All test results are recorded in a batch journal/batch report, and the batch is certified and released by the qualified person.

These production, filling, analysis and release processes have been through a validation process where all steps are checked and validated before production is authorized. Consequently, these steps are carried out according to the requirements of the Good Manufacturing Practice.

The above processes are subject to periodic audits by both gas companies and competent authorities to ensure compliance to the manufacturing and marketing authorisations.

5 Internal condition of compressed gas cylinders

New cylinders manufactured in accordance with the regulations mentioned in Section 3 have to fulfil the requirements regarding the internal surface. For example, this is defined in EN ISO 9809-1 and states "*The surface of the metal and in particular of the inner wall shall be completely clean, dry and free from oxidation products, corrosion, scale etc., since these could obscure other more serious defects. Where necessary, the surface should be cleaned under closely controlled conditions by suitable methods before further inspection "* [2].

New cylinders undergo 100% inspection.

During the operational life of the cylinder, the internal condition of a cylinder is maintained by the gas industry by a number of measures including:

- The medicinal gases filled into the cylinders have a low moisture content typically less than 67ppm. The quality of the gas is batch controlled in accordance with Local Pharmacopeia. see Section 4.
- Cylinders need to be retested periodically according to standards referenced in the regulations. During the retest a check of the inner surface is mandatory.

The above actions are intended to prevent a gas cylinder from becoming unduly contaminated with corrosion products under normal operational conditions in line. The long-term experience of the gas industry has confirmed this.

At the same time the conclusion needs to be made less absolute because it refers to visible contamination products only.

Considering the issue on a molecular level it seems likely that marginal, and not visible, contamination cannot be fully excluded, and may be present on the internal surface. For example, there could be remaining loose metal particles from the manufacturing process or chemical reaction products that have been created by elements present in a cylinder like iron oxide. Such particles can be expected in different sizes below and above the aerodynamic equivalent diameter, that is airborne and not floating particles.

From a physical view point, there is no laminar or turbulent flow inside of a gas cylinder during gas withdrawal, except the geometrical area nearby the neck thread of the cylinder. The gas molecules in the pressure chamber are simply expanding whilst gas is being withdrawn. For that reason, particles which have enough mass to overcome the buoyancy would remain inside a gas cylinder, simply fixed to the bottom by gravity. Nevertheless, airborne particles have been covered by the analytical tests described in Section 7.

6 Pharmacovigilance

EIGA member companies have, through their pharmacovigilance systems, carried out a detailed search of any reports arising from inhalation of particles dropping out of the gas cylinder and coming into the inhalation stream. In particular, a search was performed in the pharmacovigilance database of one manufacturer for all oxygen post-marketing cases using the SMQ (Standard MedDRA Query) “Oropharyngeal disorders”.

In their most recent Periodic Safety Update Reports (PSUR), the EIGA member companies considered that the benefit-risk balance of medicinal gases, regardless of their packaging, remains unchanged, as being favourable.

7 Testing of medicinal oxygen from gas cylinders (Best Operating Practice from EIGA and/European countries)

Patient safety is of paramount importance to the medicinal gases industry and considerable investments are made to ensure that the outstanding record of patient safety is maintained. As part of their ongoing efforts to ensure patient safety EIGA Member companies carried out a series of tests to confirm the quality of the delivered product in relation to any particle carryover. Prior to the study, EIGA Member companies were not aware of any instances of particle migration from medicinal gas cylinder packages, and the objective of the tests was to confirm that particle migration is not a concern.

7.1 Test objectives

The objective of the study was to:

- Quantify the levels of metal particles from medicinal gas cylinder packages; and
- Evaluate the results with respect to applicable standards.

The typical alloy of seamless steel gas cylinders is 34CrMo4. The main elements of this alloy are chromium, (Cr) iron, (Fe), molybdenum, (Mo) and nickel, (Ni). These were chosen to be analysed.

This work was carried out by the total emptying of 10 L and 50L gas-filled cylinders supplied by EIGA Members, thereby providing sufficient sampling volume to ensure a very low specific detection limit.

Two scenarios regarding the condition of the internal surface of the sample cylinders have been considered:

- Cylinders with clean surfaces and no corrosion (standard operational condition); and
- Cylinders with heavy corrosion (worst case scenario).

The samples of gas cylinders containing medical-grade oxygen gas were provided by different gas providers. Each cylinder was equipped with a pressure regulator and flowmeter. The references and the associated flowmeter regulators are given in Table 1.

7.2 Cylinder selection

Cylinders were selected on a number of criteria, and these included:

- Smaller cylinders, less than 10 litres have not been tested as usually small cylinders are used in ambulances, in emergency situations or for transport of patients within the hospital area. Consequently the use is only for short treatment periods of less than one hour, hence the daily exposure is much lower than in the case of long term treatment where it is most probable that cylinders greater than or equal to 10 litres are used. The 10 litre cylinder is the most commonly used medicinal gas cylinder by gas-companies.
- Sampling of cylinders was not based on a randomized selection of cylinders or a specific risk assessment, as the aim of the study was to check:

- best case scenario (no corrosion inside the cylinders); and
- the worst case scenario (heavily corroded cylinders).

The sample cylinders for the worst case scenario were either from in service cylinders or artificially corroded cylinders. By including the two scenarios above, the same or lesser degree of metallic impurities were covered.

- The selection of the cylinders to be tested, depend only on the degree of the internal surface corrosion and the water capacity of the cylinder for example 10 litre and/or 50 litre. Additionally, it was decided that all cylinders would be equipped with a residual pressure valve. All other criteria listed in the tables, such as the date of first service or date of last periodic inspection are only for information.

Note: Most medical oxygen cylinders in Asia are currently not equipped with RPVs.

Table 1 Description of cylinders and equipment used for particle measurement

	Cylinder code	Cylinder water capacity	Date of first service	Date of last periodic inspection	Valve type	Pressure regulator
1st batch	K93.1	50L	1979	May 2015	RPV type; no filter	Medical type with flowmeter ; 60µm filter
	K93.2	50L	1987	May 2015	RPV type; no filter	Medical type with flow meter ; 60µm filter
	K93.3	50L	1981	May 2015	RPV type; no filter	Medical type with flow meter ; 60µm filter
	J62.1	50L	2007	April 2016	RPV type; no filter	Medical type with flow meter ; 60µm filter
	J62.2	50L	2007	April 2016	RPV type; no filter	Medical type with flow meter ; 60µm filter
	J62.3	50L	2006	April 2016	RPV type; no filter	Medical type with flowmeter ; 60µm filter
	L89.1	10L	1973	May 2016	RPV type; no filter	Medical type with flow meter ; 75µm filter
	L89.2	10L	1986	May 2016	RPV type; no filter	Medical type with flow meter ; 75µm filter
	L89.3	10L	1961	May 2016	RPV type; no filter	Medical type with flow meter ; 75µm filter
2nd batch	K93.4	10L	1980	Sept. 2012	RPV type; no filter	Medical type with flow meter ; 80µm filter
	K93.5	10L	1985	Dec. 2007	RPV type; no filter	Medical type with flow meter ; 80µm filter
	K93.6	10L	1975	Feb. 2011	RPV type; no filter	Medical type with flow meter ; 80µm filter
	J62.4	10L	1999	April 2010	RPV type ; no filter	Medical type with flow meter ; 80µm filter
	J62.5	10L	1997	April 2008	RPV type ; no filter	Medical type with flow meter ; 80µm filter
	J62.6	10L	1998	Jan. 2008	RPV type ; no filter	Medical type with flow meter ; 80µm filter
	L89.4	10L	1977	Sept. 2012	RPV type; no filter	Medical type with flow meter ; 80µm filter
	L89.5	10L	1977	Sept. 2012	RPV type; no filter	Medical type with flow meter ; 80µm filter
	L89.6	10L	1977	Jan. 2008	RPV type; no filter	Medical type with flow meter ; 80µm filter

7.3 Sampling method

The impurity sampling procedure was performed in the usual conditions of use of medicinal gas cylinders: expansion and total emptying of medicinal oxygen, in the laboratory, at a controlled flow-rate of 15 L/min and at room temperature (20°C). Pressure regulators dedicated to medical oxygen distribution were installed on the sample cylinders. Oxygen filtration was performed with polyvinylidene fluoride (PVDF) membranes with a 0.22 µm porosity (Millipore) installed in Teflon PFA Savillex® filter holders. The oxygen transfer tubes, from the pressure regulator up to the filtration unit, were also made with Teflon™ PFA.

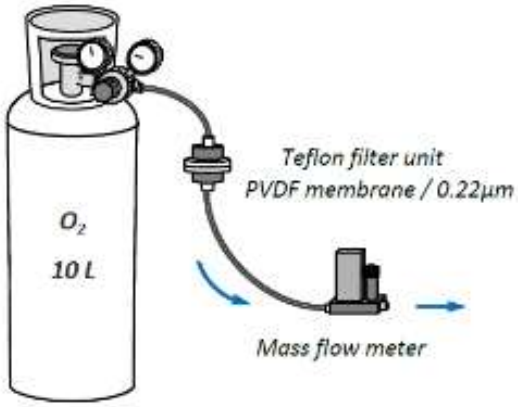

Figure 4 Schematic of equipment used for expansion and filtration of oxygen cylinders

Figure 5 Laboratory installation

Figure 6 Laboratory installation

Before sampling, all the materials used (including PVDF membranes) were decontaminated following a strict cleaning protocol dedicated to ultra-trace metal analysis: successive soaking and cleaning in 10 % nitric solutions, rinsing with ultrapure water (18Mohm.cm, Millipore) and drying in a laminar flow hood.

The measurements were performed in a clean room according to Class ISO7 of EN ISO 14644-1 *Cleanrooms and associated controlled environments. Classification of air cleanliness by particle concentration* [8] to guarantee no contamination of the collected filters by the environment.

Before expansion of the sample cylinders, a series of sampling blanks was performed on the Savillex® filtration unit, equipped with PVDF membranes, by argon flushing (99.999% quality) at the same flow-rate conditions as those used for samples (15 L/min). PVDF filters were weighed before and after sampling and drying (24 h under a laminar flow hood) to estimate the mass of sampled particles.

Expansion flow-rates of each sampled and filtrated cylinder were adjusted using the flowmeter regulator at a flow-rate of 15 L/min and controlled during expansion with a flowmeter produced by Bronkhorst.

A flow-rate of 15 L/min was chosen because this represents the typical highest flow rate that can be selected on pressure regulators for medicinal oxygen use. Therefore, it is assumed that higher flow rates can be associated with a higher risk of airborne particles.

7.4 Analysis results

Analyses were performed in two steps. Filters containing the impurities were acid dissolved and then chromium, molybdenum, nickel and iron concentrations in the acid were determined by extracts by inductively coupled plasma mass spectrometry (ICP-MS).

PVDF filters containing impurities were digested with concentrated nitric, hydrochloric and hydrofluoric acids with a high purity grade. This mixture was then heated using thermo-regulated heating blocks (DigiPrep SCP Sciences) for 3 h at 90°C. After cooling, acid extracts were diluted in ultrapure water (18.2 MΩ.cm, Millipore).

Taking into account the expected low levels of metallic impurities, the analytical technique retained was ICP-MS (Thermo Scientific Xseries2). This technique is a multi-elemental method and is considered as the most sensitive for elemental analysis allowing the quantification of concentration levels as low as some ng/L in liquid solution.

External calibration solutions from 0.1 to 20 µg/L containing iron, chromium, nickel and molybdenum were prepared with acid matrix matching for ICP-MS element quantification. An internal standard was added (rhodium) with a 1 µg/L concentration in all the analysed samples (including analytical blanks) in order to prevent potential instrument drifts. The 52Cr, 56Fe, 60Ni, 95Mo and 103Rh isotopes were monitored with a 50 ms measurement time and a number of replicate per measurement of 3. A collision-reaction device containing a mixture gas of hydrogen 7% diluted in helium was used in order to prevent analysis from potential interferences.

Results obtained for the mass of impurities sampled and their iron, chromium, nickel and molybdenum content are presented in Table 3.

Table 2 Particle measurements Scenario 1 9 sample results and scenario 2 6 sample results

	Cylinder code	Total particle mass (g)	Initial pressure (bar)	Average flow rate (L/min)	Total mass by element collected on the filter after complete gas withdrawal (µg/filter)			
					Cr	Fe	Ni	Mo
1st batch	K93.1	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	K93.2	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	K93.3	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	J62.1	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	J62.2	< 0,001	200	15	< 0,05	< 0,5	0.080	< 0,01
	J62.3	< 0,001	200	15	< 0,05	0.63	< 0,05	< 0,01
	L89.1	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	L89.2	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	L89.3	< 0,001	200	15	< 0,05	< 0,5	< 0,05	< 0,01
	Detection limit	0,001			0.05	0.5	0.05	0.01
2nd batch	K93.4	< 0,001	180	15.7	< 0,05	< 0,5	< 0,05	< 0,01
	K93.5	< 0,001	180	15.9	< 0,05	< 0,5	< 0,05	< 0,01
	K93.6	< 0,001	180	15.6	< 0,05	< 0,5	< 0,05	< 0,01
	J62.4	< 0,001	180	15,9	< 0,05	< 0,25	< 0,05	< 0,01
	J62.5	< 0,001	180	16,0	< 0,05	< 0,25	< 0,05	< 0,01
	J62.6	< 0,001	180	16,0	< 0,05	< 0,25	< 0,05	< 0,01
	L89.4	< 0,001	180	16.0	< 0,05	< 0,5	< 0,05	< 0,01
	L89.5	< 0,001	180	16.1	< 0,05	< 0,5	< 0,05	< 0,01
	L89.6	< 0,001	180	16.0	< 0,05	< 0,5	< 0,05	< 0,01
	Detection limit	0.001			0,05	0,5	0.05	0.01

In addition, the pictures in 7.4 show corresponding endoscopic observations performed inside the cylinders used for particle measurement tests. Pictures were taken after particle analyses were carried out.

7.5 Internal observations of cylinders (cylinder bottom and walls), Cylinder pictures (Batch 1)

All cylinders were photographed externally and internally.

7.5.1 Cylinders from company K93

Figure 7 External view of cylinders 1,2, and 3 from company K93

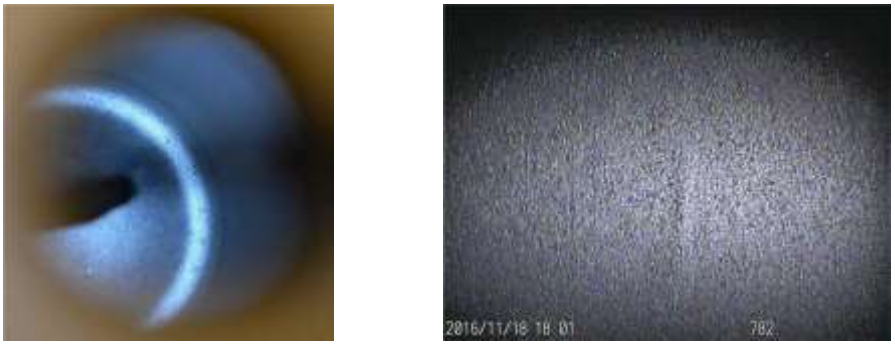

Figure 8 Internal views of cylinder K93.1

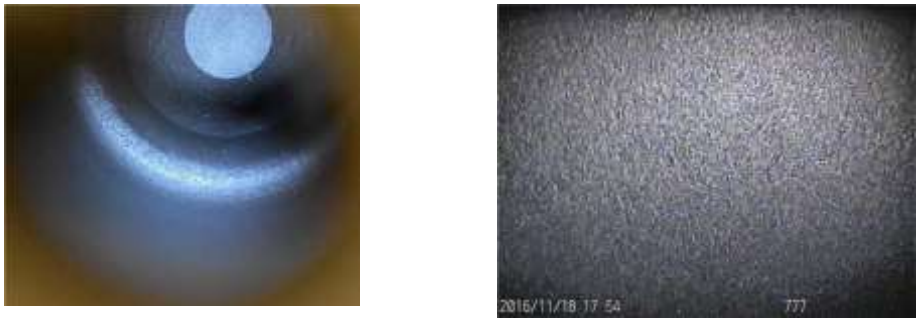

Figure 9 Internal views of cylinder K93.2

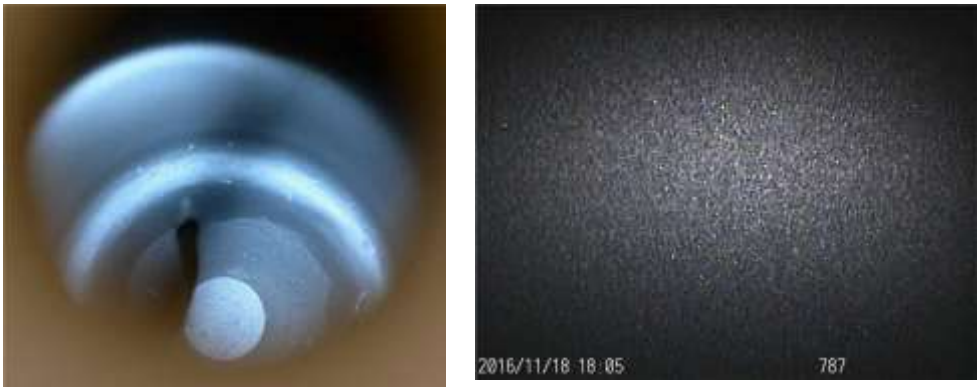

Figure 10 Internal views of cylinder K93.3

No visual corrosion and no internal superficial oxidation.

7.5.2 Cylinders from company J62

Figure 11 External view of cylinders 1,2, and 3 from company J62

Figure 12 Internal views of cylinders J62.1

Figure 13 Internal views of cylinder J62.2

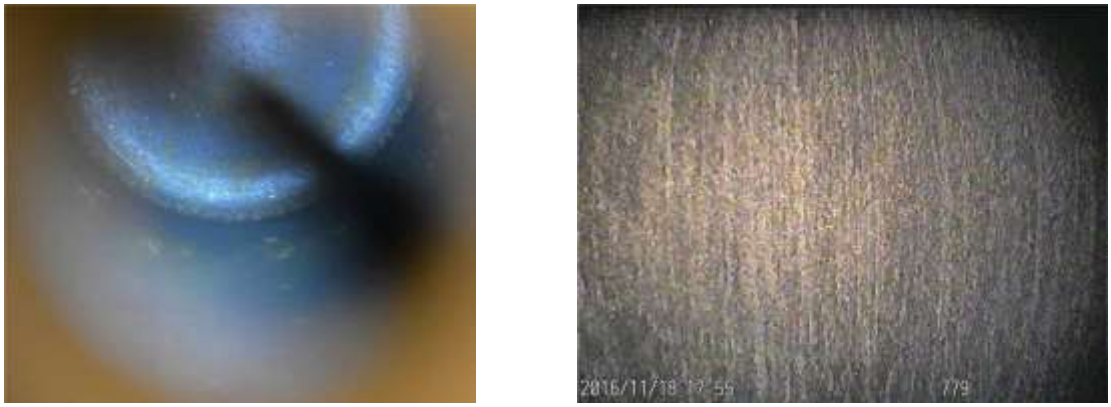

Figure 14 Internal views of cylinder J62.3

No visual corrosion phenomenon and slight internal superficial oxidation.

7.5.3 Cylinders from company L89

Figure 15 External views of cylinders 1, 2 and 3 from company L89

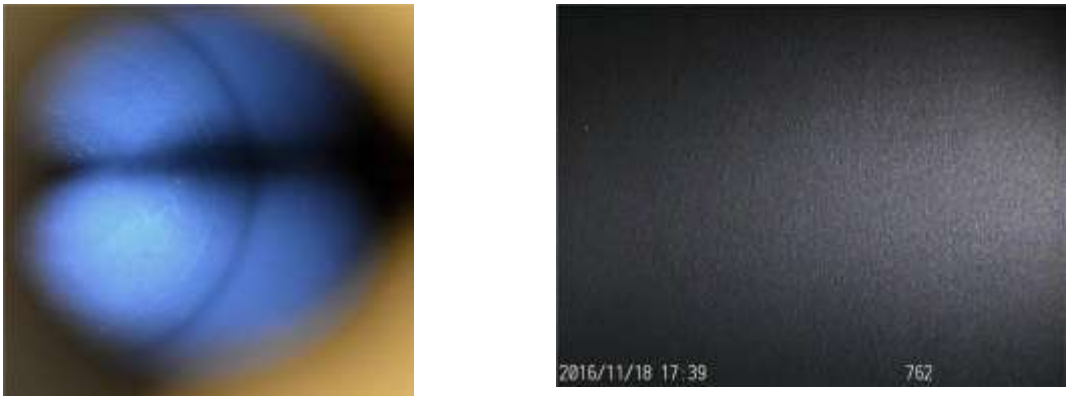

Figure 16 Internal views of cylinder L89.1

Figure 17 Internal views of cylinder L89.2

Figure 18 Internal views of cylinder L89.3

No visual corrosion phenomenon and no internal superficial oxidation, with several indications of corrosion pits at the bottom surface and slight corrosion pits on the cylindrical part of L89.3 cylinder (from shot blasting cleaning).

7.6 Internal observations of cylinders (cylinder bottom and walls), Cylinder pictures (Batch 2)

7.6.1 Cylinders from company K93

Figure 19 External view of cylinders 4, 5, and 6 from company K93

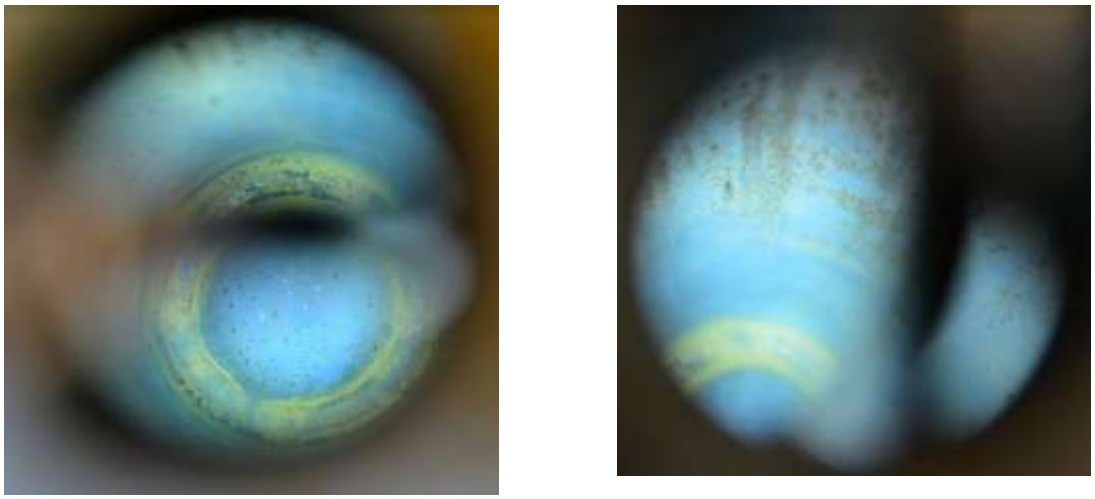

Figure 20 Internal views of cylinder K93.4

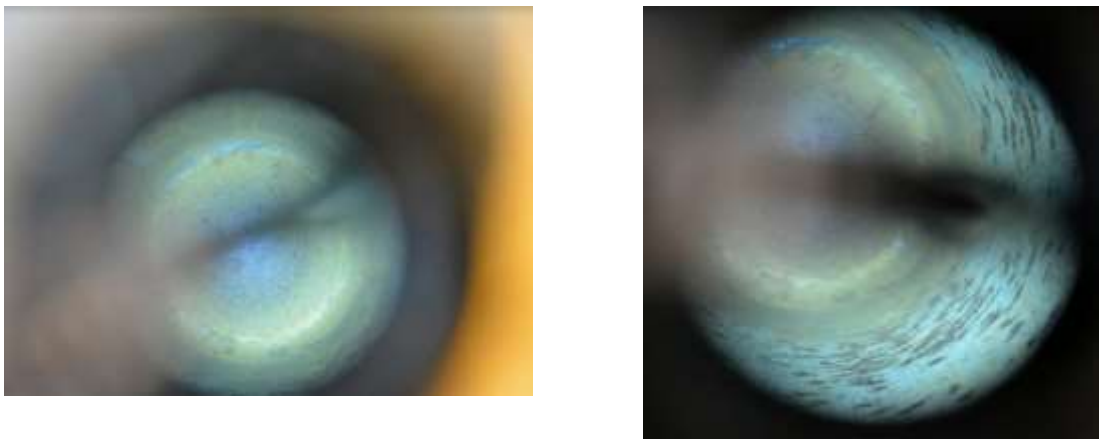

Figure 21 Internal views of cylinder K93.5

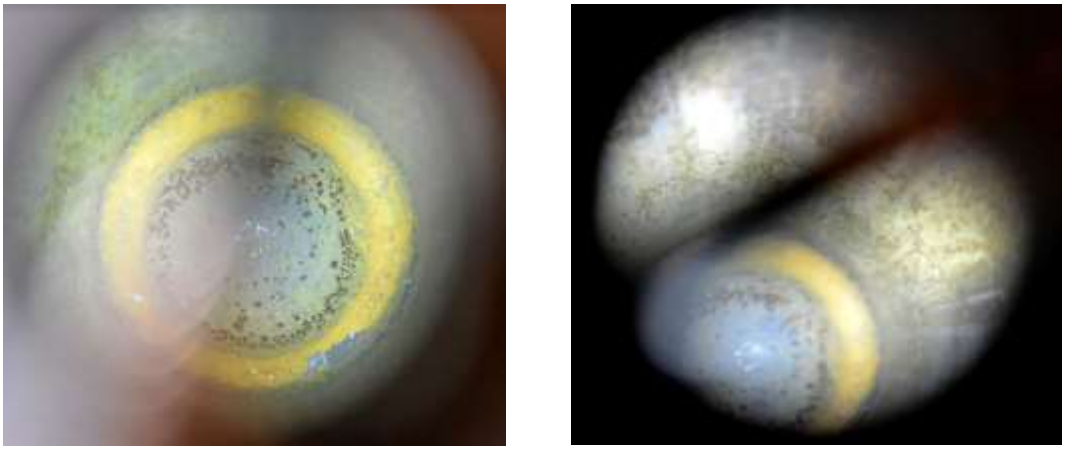

Figure 22 Internal views of cylinder K93.6

Strong internal superficial oxidation in all 3 cylinders, at the bottom surface as well as on the cylindrical part.

7.6.2 Cylinders from company L89

Figure 23 External view of cylinders 4, 5, and 6 from company L89

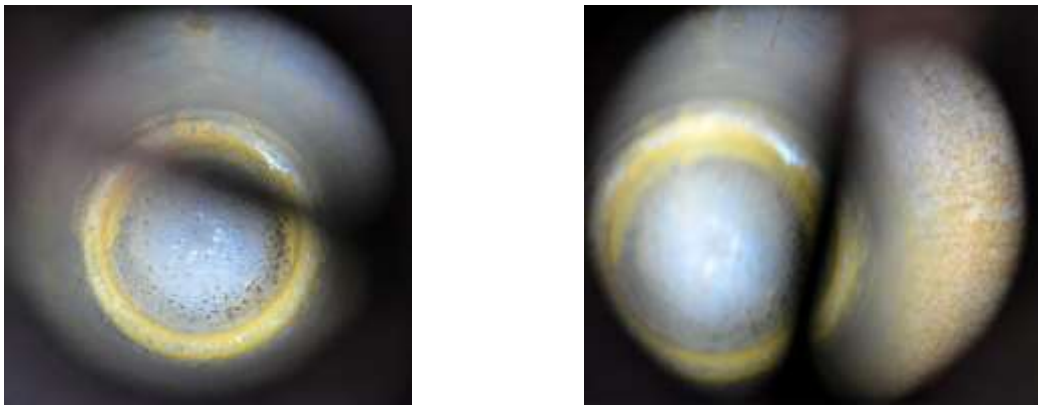

Figure 24 Internal views of cylinder L89.4

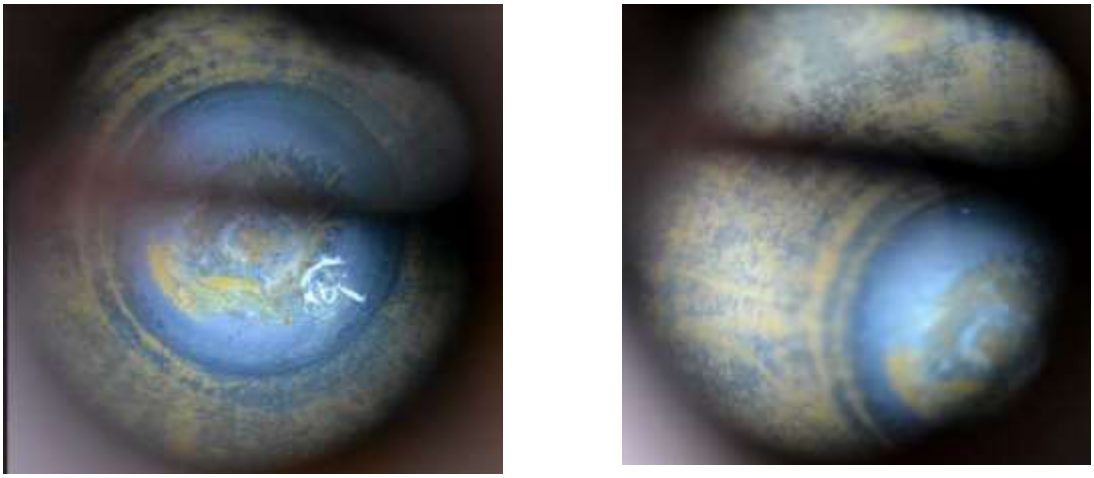

Figure 25 Internal views of cylinder L89.5

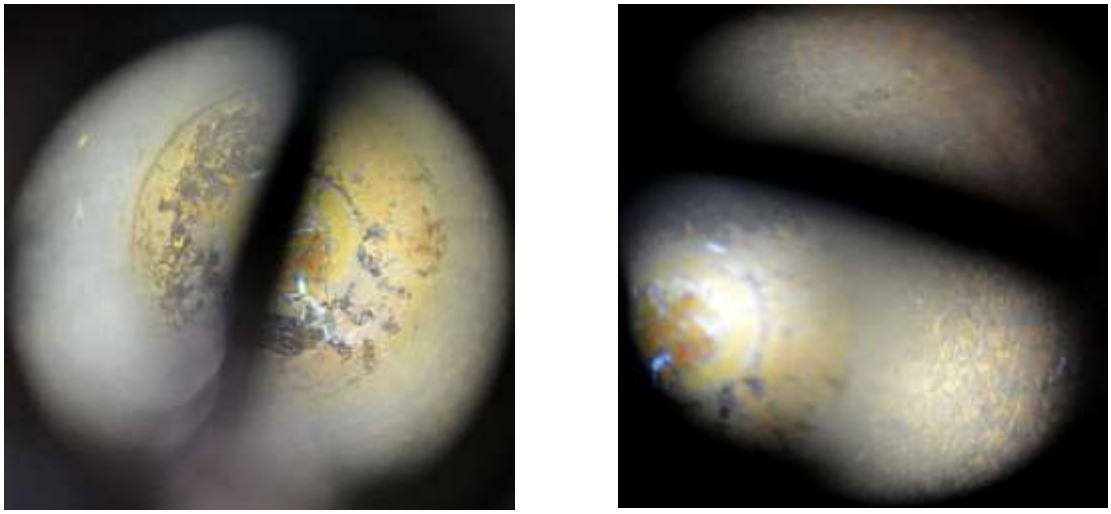

Figure 26 Internal views of cylinder L89.6

Strong internal superficial oxidation in all three cylinders, at the bottom surface as well as on the cylindrical part.

Impurities mass measurements show a very low impurity contamination of the oxygen flow, even for the worst-case scenario where cylinders showing heavily oxidised internal surfaces could be found.

7.7 Discussion of analytical results

In 2015 the European Medicines Agency issued a new document ICH Q3D *Guideline on Elemental Impurities* [9] which has become part of the legal pharmaceutical framework of Europe. The guideline is mandatory for new market authorizations and will become mandatory for existing market authorizations by year end 2017.

The guideline considers toxicological aspects of metallic impurities of medicines, taking into account three different routes how a medicine can be administered to humans. These are oral, parental and inhalative application. For each application the guideline defines a permitted daily exposure, PDE, which defines the maximum amount of a specific element allowed to be in a drug without having negative impacts to humans.

Whilst there is no information available on how to apply the ICH Q3D Guideline to medicinal gases, this publication describes EIGA's interpretation based on the inhalation of medicinal gases.

Iron (Fe) is mentioned in the guideline, but not listed with a PDE due to its low inherent toxicity. The results for iron show that all results are below the detection limit except one at a very low concentration. Chromium and molybdenum were all measured below the detection limits and below the ICH Q3D guidelines thresholds.

The only element that is mentioned in the guideline and was detected in one probe of the sample cylinders is nickel. The PDE for this element is 5 µg/day for inhalation. The value measured in one cylinder with an oxygen content of 1,926 m^3 (10l, 180 bar, 15°C) was 0,08 µg, leading to a specific contamination of 0,0415 µg/m^3.

Medicinal oxygen is administered to patients for a number of reasons. Table 3 shows typical application data and some related calculations.

Table 3 Application data and related calculations

	Oxygen flow (l/min)	Time	Oxygen volume (m^3)	Ni contamination (µg/m^3)	Ni to patient (µg)	PDE (µg/day)	Ni/PDE (%)
Situation							
First aid	15	30 min	0,45	0,0415	0,0187	5	0,37
Home care	5	24hrs	7,2	0,0415	0,2991	5	5,98
Worst case (not realistic)	20	24hrs	28,8	0,0415	1,1963	5	23,93

NOTE 1 It is assumed the gas withdrawn from the cylinder is inhaled by the patient at 100%, i.e. no gas escaping to the ambient.

NOTE 2 The flow level of 20 l/min in the worst-case scenario was derived from the ICH Q3D guideline.

Two conclusions can be drawn from the data.

- The presence of analysed particles in the gas is clearly below critical values; and
- The presence of analysed particles in the gas is even less than 30% of the PDE. According to the ICH Q3D guideline this allows to produce such medicines without additional monitoring and/or analytical controls.

8 Conclusions

Taking into account the results presented above EIGA and AIGA members are of the opinion that the risk benefit balance can be deemed as favourable for medicinal gas packages supplied by EIGA and AIGA Member companies. Toxicology levels have proven to be far below the values given in the ICH Q3D guideline. For iron, in any case, measured levels were undetectable or very low. This shows that there are no related risks for patients in the inhalation of medicinal oxygen from steel/aluminium alloy cylinders.

9 References

Unless otherwise specified, the latest edition shall apply.

[1] EN 1964-1, *Transportable gas cylinders. Specification for the design and construction of refillable transportable seamless steel gas cylinders of water capacities from 0,5 litre up to and including 150 litres. Cylinders made of seamless steel with an Rm value of less than 1100 MPa* www.cen.eu

[2] ISO 9809-1 *Gas cylinders -- Refillable seamless steel gas cylinders -- Design, construction and testing -- Part 1: Quenched and tempered steel cylinders with tensile strength less than 1 100 MPa* www.iso.org

[3] Directive 2010/35/EU - *of 16 June 2010 on transportable pressure equipment and repealing Council Directives 76/767/EEC, 84/525/EEC, 84/526/EEC, 84/527/EEC and 1999/36/EC* www.europa.eu

[4] ADR *European Agreement concerning the International Carriage of Dangerous Goods by Road* www.unece.org

[5] EN ISO 10297, *Gas cylinders - Cylinder valves -Specification and type testing*, www.cen.eu

[6] EN ISO 10524-3, *Pressure regulators for use with medical gases. Pressure regulators integrated with cylinder valves* www.cen.eu

[7] EN ISO 15966 *Gas cylinders. Residual pressure valves. General requirements and type testing*. www.cen.eu

[8] EN ISO 14644-1 *Cleanrooms and associated controlled environments. Classification of air cleanliness by particle concentration* www.cen.eu

[9] *ICH Q3D Guideline on Elemental Impurities* www.ich.org

10 Other References

EN 1968 Transportable gas cylinders. Periodic inspection and testing of seamless steel gas cylinders

EN 1802 Transportable gas cylinders. Periodic inspection and testing of seamless aluminium alloy gas cylinders