# ICH Q3D RISK ASSESSMENT REPORT ELEMENTAL IMPURITIES IN MEDICINAL GASES

## AIGA 115/25

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# ICH Q3D RISK ASSESSMENT REPORT ELEMENTAL IMPURITIES IN MEDICINAL GASES

As part of a programme of harmonisation of industry standards, the Asia Industrial Gases Association (AIGA) has published AIGA 115, *ICH Q3D Risk Assessment Report Elemental Impurities in Medicinal Gases,* jointly produced by members of the International Harmonization Council and originally published by European Industrial Gases Association (EIGA) as EIGA Doc 216, *ICH Q3D Risk Assessment Report Elemental Impurities in Medicinal Gases.*

This publication is intended as an international harmonised publication for the worldwide use and application by all members of the International Harmonisation Council whose members include the Asia Industrial Gases Association (AIGA), Compressed Gas Association (CGA), European Industrial Gases Association (EIGA), and Japan Industrial and Medical Gases Association (JIMGA). Each association's technical content is identical, except for regional regulatory requirements and minor changes in formatting and spelling.




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**Amendments to 115/21**

| Section | Change |
|---|---|
| 2.1, 4.1, 7 & Appendix A | Extended to cover argon and argon/oxygen mixtures |

NOTE Technical changes from the previous edition are marked with a line in the left margin

## 1 Introduction

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has developed a harmonised guideline for elemental impurities (EIs), Q3D in pharmaceutical products which includes medical gases, referred to as ICH Q3D [1] [1].

ICH Q3D recommends a science and risk-based approach to evaluate the potential for introduction of EIs into the drug product and to determine if additional controls need to be included in the overall control strategy to ensure product quality and safety. The overall process follows the sequence *identify*, *evaluate* and *summarise*.

To determine whether medicinal gases are likely to contain any EIs, specified in ICH Q3D, EIGA members performed a risk assessment (RA) which considered which EIs could theoretically be present in the licenced drug products. The maximum daily dosages (MDD) were also calculated for each medicinal gas to determine which medicinal gases were at the highest risk, see Section 4.

Although the method of production is unique for each medicinal gas, the method of filling and packaging the gases is common across all products. The same basic equipment and procedures are used to fill these products and the container closure systems (CCS) used are similar for all products. This led to a conclusion that the potential EIs present was common for all medicinal gases.

For those high risk EIs that were identified as potentially being present in the gases, appropriate test procedures were set up to determine their levels in the finished product.

The test method sampling system took product from the CCS so as to represent the gas that would be delivered to the patient for treatment. This was considered to be the worst-case scenario for all medicinal gases and gas mixtures, to determine whether the EIs would be within the permitted daily exposure (PDE) limits detailed in ICH Q3D.

From the information given in this report, the view of the AIGA companies is that the levels of EIs within the medicinal gases that they supply for patient treatment are well below the limits set out in ICH Q3D.

As and when new information becomes available, this interpretation shall be reviewed as required.

NOTE—ICH Q3D R2 issued April 26 2022 was assessed on necessity for amendments – outcome no amendments necessary, as for the inhalation route only Gold, Silver and Nickel PDEs where changed and the PDEs are now higher than in the previous version. Tables for Nickel have not been adapted to the new higher limit.

## 2 Scope and purpose

### 2.1 Scope

The scope of this publication covers all packaged medicinal gases as listed below produced by AIGA members and approved as designated medical gases by the U.S. Food and Drug Administration (FDA) or authorised as medicinal products in other country jurisdictions. It covers both compressed and liquefied gases, supplied in high pressure cylinders as well as cryogenic liquids, supplied either by tankers into bulk storage tanks or in portable cryogenic containers. It considers all manufacturing processes, including the starting materials used, as well as the CCS used to supply these medicinal gases for patient use.

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 either 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.

This publication covers all licensed medicinal gases currently supplied by EIGA, CGA, AIGA, and JIMGA members or gases being monographed in one of the Pharmacopoeias within the jurisdiction of the

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

members, which are as follows:

- oxygen;
- synthetic medical air;
- medical air;
- carbon dioxide;
- nitrous oxide;
- nitrogen;
- xenon;
- helium;
- argon:
- nitrous oxide/oxygen mixtures (normally 50/50 mixture);
- nitric oxide in nitrogen (normally up to 1000 ppm nitric oxide in nitrogen);
- helium/oxygen mixtures (normally 80/20 mixture);
- carbon dioxide/oxygen mixtures (normally 5% but in some cases up to 20% carbon dioxide in oxygen);
- methane/acetylene/carbon monoxide and oxygen in nitrogen (normally up to 0,3% of each component with 21% oxygen in nitrogen) referred to as lung function mixture; and
- argon/oxygen mixtures (normally up to 80/20).

**NOTE—Argon is not classified as a designated medical gas in the United States.**

It considers all manufacturing processes including any starting materials used, up to the filling of the medicinal gas into the CCS or into the customer's bulk storage tank.

It does not cover medicinal gases that are produced using on-site manufacturing equipment such as pressure swing adsorption (PSA) or air compressing plants on the customer's premises.

It does not include particles that could be added by the equipment connected by the customer, and only covers the manufacturing process.

### 2.2 Assumptions

The assumptions used in this publication include:

- Any EIs specified in the ICH Q3D guidelines will only be present as particulate in the medicinal gases. The only exception to this is mercury that could be present as a gaseous impurity, but there were no risks identified where it was likely to be present; and
- The likelihood of entrainment of particles in medicinal gases supplied as cryogenic liquids, vaporised prior to use, is significantly lower than the potential for particles in compressed gases. The liquefied gases are stored at low pressure and the particles tend to remain in the liquid phase.

### 2.3 Purpose

This publication is intended to be used as the basis for the product risk assessment for all EIGA, CGA, JIMGA, and AIGA member companies to produce to cover all their current authorised Medicinal Gases, to demonstrate compliance with the requirements for EIs, as defined in ICH Q3D.

The publication provides the documented evidence that, under the worst-case scenario, the limits set out for EIs in the ICH Q3D Guideline will not be exceeded for the medicinal gas products in 2.1.

Where companies use different manufacturing and packaging processes than those described in this document, they will need to perform a separate risk assessment to ensure that the new processes do not introduce any additional risks that may impact on the quality of the product.

## 3 Definitions

For the purpose of this publication, the following definitions apply.

### 3.1 Publication terminology

#### 3.1.1 Shall

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

#### 3.1.2 Should

Indicates that a procedure is recommended.

#### 3.1.3 May

Indicates that the procedure is optional.

#### 3.1.4 Will

Is used only to indicate the future, not a degree of requirement.

#### 3.1.5 Can

Indicates a possibility or ability.

### 3.2 Definitions according ICH Q3D

#### 3.2.1 Container closure system (CCS)

In addition to the definition given in ICH Q3D, for compressed medicinal gases, the CCS means the high-pressure cylinder and the cylinder valve, which may include the pressure regulator, with integrated flow and pressure outlets (VIPR). For cryogenic medicinal gases, the CCS means the insulated container and valve.

#### 3.2.2 Daily dose

The total mass of drug product that is consumed by a patient on a daily basis.

#### 3.2.3 Permitted daily exposure (PDE)

The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

## 4 AIGA's approach

### 4.1 Maximum daily doses

To determine the potential maximum daily doses (MDD) for different medicinal gases, the maximum human respiratory volume, see Table A.1.1 of ICH Q3D, is calculated at 28,800 litres per day. This relates to a continuous breathing volume of 20 litres per minute, which is not a realistic volume.

To determine an appropriate MDD, account needs to be taken of the volume of the lungs and the number of breaths that a patient will take (on a continuous basis). The tidal volume (TV) for the lungs is represented by the volume of air that the lungs will displace between normal inhalation and exhalation when there is no extra effort applied.

In a healthy young adult, the TV is approximately 500 ml per inspiration and the normal respiratory rate is between 12 and 18 breaths per minute, that is an average of 15 breaths per minute. For patients with respiratory disease, the respiratory rate can be higher than 18 breaths per minute, but the TV will tend to be lower. Taking this into account, the average MDD can be calculated as a TV of 500 ml multiplied by 15 breaths per minute, which equates to 7.5 litres per minute or 10800 litres per day.

Hence, for all calculations, the MDD is calculated as 10800 litres per day. This is considered the worst-case scenario, as this volume is seen as a MDD which will only be administered as a short-term treatment.

Medical oxygen is the only medicinal gas therapy where long term treatment will be prescribed to the patient, 30 days or more, as specified in ICH Q3D. Those patients on long term oxygen therapy are likely to be prescribed an equivalent daily dosage that is significantly lower than MDD described.

**Table 1—Maximum daily doses for medicinal gases**

| Product | Calculation / Explanation | Maximum Daily Dose |
|---|---|---|
| Oxygen | The MDD applies to acute treatment. | Acute treatment 10800L |
| Synthetic medical air | For air the same assumptions can be made as for oxygen, for acute treatment nevertheless as air is not used for long term treatment in chronically ill patients. | Acute treatment 10800L |
| Medical air | See synthetic medical air. | Acute treatment 10800L |
| Carbon dioxide | Pure $CO_2$ cannot be inhaled, therefore if we consider 5% $CO_2$ in oxygen as the maximum breathable mixture and the total treatment time per day with always less than 1h, is 22,5L. | Acute treatment 22,5L |
| Nitrous oxide | Nitrous oxide for anesthetics is used with a concentration of $N_2O$ up to 70% in oxygen. The maximum duration of treatment is 10h, resulting in 3150L. | Acute treatment 3150L |
| Nitrogen | Pure nitrogen cannot be inhaled, the maximum volume of nitrogen in mixtures can be found in synthetic medical air. Considering the specification for synthetic medical air (with maximum concentration of 79% for $N_2$), the MDD is 8532L. | Acute treatment 8532L |
| Xenon | For xenon, when used as an anesthetic, the same calculation can be used as for nitrous oxide. The maximum treatment duration is 6h, therefore resulting in 1890L. | Acute treatment 1890L |
| Helium | Pure helium cannot be inhaled. If we consider 80% He in $O_2$ as the maximum breathable mixture, this would result in an inhalation mixture of 8640L for 24hrs used. | Acute treatment 8640L |
| Argon | Pure argon cannot be inhaled. If we consider 80% argon in oxygen as the maximum breathable mixture, this would result in an inhalation mixture of 8640 L for 24hrs used. | Acute treatment 8640L |

| Product | Calculation / Explanation | Maximum Daily Dose |
|---|---|---|
| Nitrous oxide/Oxygen mixtures | See nitrous oxide and oxygen, but as the mixture is not 70% nitrous oxide but only 50%, for short term treatment using the analgesic effects, the results are 2250L for $N_2O$ and 2250L for oxygen. So 4500L in total for the mixture. | Acute treatment 4500L |
| Nitric Oxide/Nitrogen mixtures | 40 ppm of NO is the maximum dose given to the patient, Considering the minimal dose of nitric oxide in the finished product (considered as 200 ppm), this leads to the highest consumption of the mixture. The gas is delivered with 20% of the MDD for oxygen – therefore 2160L of the mixture would be used.<br>Inhaled nitric oxide has been given for time periods up to 7 days in the perioperative setting, but common treatment times are 24-48 hours. Normal dosages in adults are 20 ppm or less. | Acute treatment 2160L (this equates to 4,32L of pure NO) |
| Helium/Oxygen mixtures | See helium with 8640L of helium and 2160L of oxygen. 10800L in total for the mixture. | Acute treatment 10800L |
| Carbon dioxide/Oxygen mixtures | See carbon dioxide with 22,5L of carbon dioxide and 450L of oxygen. 472,5L in total for the mixture. | Acute treatment 472,5L |
| Lung function mixtures | Lung function mixtures are only used for diagnostic purpose, only up to 3 - 5 breaths are taken resulting in 17,5L MDD, if we consider 3,5L as the inspiratory capacity for a single breath. | Acute treatment 17,5L |
| Argon/Oxygen mixtures | See argon with 8640L of argon and 2160L of oxygen. 10800L in total for the mixture. | Acute treatment 10800L |

### 4.2 Risk assessment

The risk assessment considered the potential sources for EIs, including:

- active pharmaceutical ingredients;
- excipients;
- medicinal gas manufacturing and filling processes;
- potential contributions of manufacturing equipment; and
- CCS, including their maintenance.

The manufacturing processes are described in Appendices A, B, C and D.

The manufacturing process for oxygen and nitrogen in air separation units also covers the production of medicinal air.

For the outcome from the original risk assessments carried out at the outset of this process see Table 2.

The only EIs that have been identified in the risk assessment as potentially being present in the medicinal gases include:

- lead (Pb);
- vanadium (V);
- nickel (Ni);

- molybdenum (Mo);
- copper (Cu);
- tin (Sn); and
- chromium (Cr).

None of these elements are intentionally added to the products or are present in the starting materials or excipients used in the manufacture. Generally, catalysts are not used in the manufacturing process, and where used do not contain any elements included in the ICH Q3D list or will be trapped within the manufacturing process.

In most cases the identified elements can be part of manufacturing equipment, as a component in stainless steel, steel or brass alloys.

The identified elements are also present in the CCS used for supplying the medicinal gases. The gases are supplied in either steel or aluminum cylinders, which are equipped with brass or stainless-steel valves. Therefore, the CCS is considered as the most critical part for medicinal gases when determining EI levels.

The source of the EIs identified as being potentially present in the finished product will only be from particles being shed by the manufacturing process or the CCS. Consideration was given to whether there was evidence of any of these elements being leached from the equipment or the CCS but there is no documented evidence that this will occur.

The CCS is considered as the most likely part of the delivery process where particulate could be present in the gas supplied to patients. It will accumulate any particulate generating in the manufacturing and transferred through filling process, as well as particulate generated within the cylinder or valve, due to use.

Therefore, the tests that were performed were to establish if any particulate was present in the finished product, when administered from the CCS, ensuring that the particulate was trapped when the gas was being delivered in a manner that would be used when treating the patient.

**Table 2—Presence of EI in the different steps in the manufacturing process**

| Element | ICH Q3D class | API Synthesis and starting material | Intentionally added | In Excipients | Coming from manufacturing equipment | Leached from CCS | Action |
|---|---|---|---|---|---|---|---|
| Cadmium (Cd) | 1 | No | No | No | No | No | No further actions |
| Lead (Pb) | 1 | No | No | No | Yes (brass) | Yes (brass valves) | Investigation through commercially available batches |
| Arsenic (As) | 1 | No | No | No | No | No | No further actions |
| Mercury (Hg) | 1 | No | No | No | No | No | No further actions |
| Cobalt (Co) | 2A | No | No | No | No | No | No further actions |
| Vanadium (V) | 2A | No | No | No | Yes (stainless steel) | Yes (stainless steel valves) | Investigation through commercially available batches |
| Nickel (Ni) | 2A | No | No | No | Yes (stainless steel and steel) | Yes (stainless | Investigation through |

| Element | ICH Q3D class | API Synthesis and starting material | Intentionally added | In Excipients | Coming from manufacturing equipment | Leached from CCS | Action |
|---|---|---|---|---|---|---|---|
| | | | | | | steel valves and steel cylinders) | commercially available batches |
| Lithium (Li) | 3 | No | No | No | No | No | No further actions |
| Antimony (Sb) | 3 | No | No | No | No | No | No further actions |
| Barium (Ba) | 3 | No | No | No | No | No | No further actions |
| Molybdenum (Mo) | 3 | No | No | No | Yes (stainless steel and steel) | Yes (stainless steel valves and steel cylinders) | Investigation through commercially available batches |
| Copper (Cu) | 3 | No | No | No | Yes | Yes (brass valves and aluminium alloy cylinders) | Investigation through commercially available batches |
| Tin (Sn) | 3 | No | No | No | Yes (brass) | Yes (brass valves) | Investigation through commercially available batches |
| Chromium (Cr) | 3 | No | No | No | Yes (stainless steel) | Yes (stainless steel valves and aluminium alloy cylinders) | Investigation through commercially available batches |

### 4.3 Worst case scenario

In order to determine the appropriate test protocols to assess the levels of EIs in medicinal gases, the outcomes from the risk assessments carried out indicated that the worst-case scenarios should include:

- Oxygen, as it is the only medicinal gas used for long term treatment;
- The manufacturing and filling process of oxygen can be used as the representative for all the medicinal gases in the scope. This can be justified as the different manufacturing processes have a similar influence on the EI in the product as no excipients or catalysts are used and when used the particulate could be trapped during the manufacturing process;
- The filling equipment used for oxygen can be used as the representative for all the medicinal gases as, for safety reasons, copper alloy pipes are used, which makes the probability for EIs to be introduced even more likely than in the other medicinal gases filling systems;
- The CCSs used for testing should utilize both aluminium alloy and steel cylinder shells and brass valve as this is the type of equipment used for all medicinal gases;
- The VIPRs used as the closure for the primary packaging of the CCS is the most likely source of particulate in the product;
- By testing the finished product, the upstream manufacturing processes of API and starting materials are covered.

Taking into account the above reasons, the worst-case scenario used to develop the testing protocol should be:

- Medical oxygen supplied as a compressed gas in high pressure cylinders;
- Test volumes should be based on a MDD of 10800 litres per day;
- Supplied in high pressure cylinders filled to at least 200 bar. These cylinders should be both steel and aluminium alloy to ensure that the cylinder material has no influence on the results;
- Using a VIPR as the valve closure for the CCS which permits the gas to be delivered at an appropriate flowrate.

The protocol required three separate medicinal gas companies to prepare and fill the sample cylinders so as to take account of the potential variance within the systems used by the different manufacturers and their specific manufacturing processes and equipment.

Each company produced their sample cylinders as part of separate commercial batches, using their normal filling equipment and the standard filling procedures. They were required to prepare three aluminium alloy and three steel cylinders from three separate batches.

The decision was to use a 10-litre water capacity cylinder for each cylinder so as to provide a sufficient volume of gas for testing. In addition, the 10 litre cylinders also ensured that the highest internal cylinder contact surface to gas volume ratio was achieved.

This scenario resulting in a total of 18 cylinders being tested for EIs identified within the risk assessment.

The choice of the VIPR as the CCS closure system was made as this allowed the gas to be delivered in the manner it would be used when administering the medicinal gas to the patient and does not require any further equipment (other than the 6 mm flexible PVC tubing). This decision meant that the results obtained were not influenced by any downstream equipment. This type of cylinder valve closure is included in the specification for the packages within the approved marketing authorisations.

To align with the results of the risk assessments the following EIs were assessed in the testing:

- Group 1 element—lead (Pb);
- Group 2A elements—vanadium (V), nickel (Ni); and
- Group 3 elements—molybdenum (Mo), copper (Cu), tin (Sn) and chromium (Cr).

## 5 Test method

In order to detect small concentrations of any of the EIs selected for testing, a large volume of gas has to be sampled.

The proposed method of testing was to pass the gas sample through a chemical trap to collect the EIs. This equipment consisted of three Drechsel bottles, see Figure 1, which were used to trap any particulate that could be present in the gas stream delivered from the cylinder. The solutions from the Drechsel bottles was used to dissolve the listed impurities to form a clear solution of known volume that can be analysed for each element by inductively coupled plasma mass spectroscopy (ICP-MS).

**Figure 1—Drechsel bottle and head**

In order to measure to the very low concentrations that are expected, it was necessary to sample a large volume of gas. The volume of gas to be sampled depended on:

- 30% limit of the PDE for each of the elements in µg/day;
- MDD volume of the gas;
- Volume of the solution for analysis; and
- ICP-MS quantification limits for each of the elements.

The volume of gas to be sampled is different for each element because of the different PDE values and the different ICP-MS quantification limits. The volume of gas to be sampled needs to be the largest of the volumes to enable the criteria for limits of detection to achieve for all elements.

Although the risk analysis was to assess the level of particulate present in the gas, the test method was selected in order to trap and identify EIs down to the atomic form, should they be present.

Table 3 shows the required sampling volumes for the elements to be tested.

NOTE—When developing the test method, the basis for the volumes were based on an MDD of 21600 litres per day. Having reviewed the clinical implications of this decision, it was recognised that the patient would only consume 10800 litres per day.

The test volumes were based on a detection limit of 1 x $10^{-7}$ µg/mL to 1 x$10^{-2}$ µg/mL, which leads to a quantification limit 0,0001 µg/mL, (except for Cu, where the limit is 0,001 µg/mL).

It also shows that for vanadium, a minimum of 360 litres of gas is needed. This led to the decision to use a 10-litre water capacity cylinder filled to at least 200 bar with oxygen and providing 2000 litres of oxygen for the test to be performed.

**Table 3—Volume of sample gas**

| Element | PDE (µg/day) | 30% PDE (µg/day) | ICP limit of quantification, (ug/ml) | Volume of gases sampled (litres) |
|---|---|---|---|---|
| Lead (Pb) | 5 | 1,5 | 0,0001 | 72 |
| Vanadium (V) | 1 | 0,3 | 0,0001 | 360 |
| Nickel (Ni) | 5 | 1,5 | 0,0001 | 72 |
| Molybdenum (Mo) | 10 | 3 | 0,0001 | 36 |
| Copper (Cu) | 30 | 9 | 0,001 | 120 |
| Tin (Sn) | 60 | 18 | 0,0001 | 6 |
| Chromium (Cr) | 3 | 0,9 | 0,0001 | 120 |

The three Drechsel bottles were used in series with the contents of the first two bottles being analysed separately. The benefit of analysing the fluids separately was that the trapping efficiency of the test method could be assessed by the relative amounts of elements found in each bottle, see Figure 2.

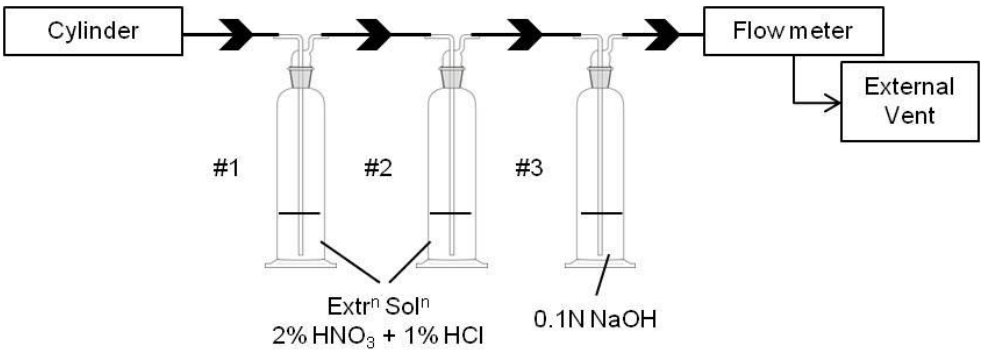



**Figure 2—Testing setup with the three Drechsel bottles**

The fluids used in the Drechsel bottles were made up of a 2% nitric acid / 1% hydrochloric acid solution (in the first two bottles) with the third using a 0.1N sodium hydroxide solution.

Each bottle used 50ml of solution.

A calibrated wet gas flow meter was used to monitor the amount of gas sampled with the flow rate set at 1L/min.

Feasibility tests carried out on a series of two open tube Drechsel bottles containing 50mL of water showed that the predicted loss of fluid in the first bubbler was about 50% (25mL) of the volume for a sample of dry gas of 1500L at 1L/min.

There was little or no loss in the second Drechsel bottle. The loss was believed to be mostly evaporative loss, with some aerosol loss into the second bubbler through the action of bubbles breaking through the surface of the fluid.

Although the basic test method, using the ICP-MS equipment is an accepted validated method of determining EIs, as detailed in ICH Q3D, it was not possible to validate the sampling method using gas standards with known concentration of the appropriate elements. It should be noted that it is not possible to produce gas standards with a known concentration of EIs.

It is also noted that other laboratories use the same method sampling the medicinal gases for EIs (see Appendix F).

The chosen laboratory used to perform the tests were accredited to EN ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories* and have been successfully inspected by the U.S. Food and Drug Administration (FDA) and the United Kingdom's Medicines and Healthcare Products Regulatory Agency [2]. The laboratory confirmed that their processes and procedures were in compliance with the methods used with Ph.Eur. Chapter 2.4.20, *Determination of Elemental Impurities* [3]. This includes the sample preparation, which is considered as critical to the success of elemental analysis.

The use of the chosen method, using Drechsel bottles and trapping the EIs in the solution was chosen due to the lower probability of the samples being contamination by external factors.

Within the initial evaluation of the test method, it was demonstrated that the first Drechsel bottle retained a finite amount of particulate and the second only retained a significantly smaller quantity, which clearly indicates the effectiveness of the method. It was also confirmed that, even if small amounts of particulate were not dissolved in the Drechsel bottle solutions, they would still be processed by the ICP-MS method, due to the high temperatures used in the instruments.

AIGA members believe that with the current knowledge the tests are performed with state-of-the-art methods and equipment sufficiently validated. Detailed method description and testing protocol.See Appendix E, the approved testing protocol.

## 6 Test results

**Table 4—Cylinder details**

| Cylinder details | | | | | | |
|---|---|---|---|---|---|---|
| **Sample cylinder ID** | **Cylinder reference No** | **Company** | **Cylinder construction** | **Cylinder capacity (Litres)** | **Cylinder filling pressure (Bar g)** | **Test date** |
| 1 | 253485SG | A | Aluminium | 10 | 230 | 17.01.2018 |
| 1A | 253485SG | A | Aluminium | 10 | n.a. | 20.07.2018 |
| 2 | 253546SG | A | Aluminium | 10 | 230 | 17.01.2018 |
| 2A | 253546SG | A | Aluminium | 10 | n.a. | 20.07.2018 |
| 3 | 253522SG | A | Aluminium | 10 | 230 | 17.01.2018 |
| 3A | 253522SG | A | Aluminium | 10 | n.a. | 20.07.2018 |
| 4 | 527870 | A | Steel | 10 | 230 | 17.01.2018 |
| 5 | 525019 | A | Steel | 10 | 230 | 17.01.2018 |
| 6 | 161616 | A | Steel | 10 | 230 | 17.01.2018 |
| 7 | 721129 | B | Aluminium | 10 | 230 | 31.01.2018 |
| 8 | 721399 | B | Aluminium | 10 | 230 | 31.01.2018 |
| 9 | 726621 | B | Aluminium | 10 | 230 | 31.01.2018 |
| 10 | 753480 | B | Steel | 10 | 230 | 31.01.2018 |
| 11 | 754021 | B | Steel | 10 | 230 | 31.01.2018 |
| 12 | 751123 | B | Steel | 10 | 230 | 31.01.2018 |
| 13 | 55255897 | C | Aluminium | 10 | 200 | 09.02.2018 |
| 14 | 55255899 | C | Aluminium | 10 | 200 | 09.02.2018 |
| 15 | 55255898 | C | Aluminium | 10 | 200 | 09.02.2018 |
| 16 | 55255895 | C | Steel | 10 | 200 | 09.02.2018 |
| 17 | 55255896 | C | Steel | 10 | 200 | 09.02.2018 |
| 18 | 55255894 | C | Steel | 10 | 200 | 09.02.2018 |

NOTE 1 MDD: 10800 litres per day

NOTE 2 Where the calibration blank has a higher count per second (CPS) than the process blanks and samples, it translates the result to a lower µg of the measured element in the solution. This can happen when the calibration blank may have had a slight amount of the element present in the solution. However, where this happens, the QC requirements can be met. The report details the actual results.

NOTE 3 As result of the first batch analysed initially showed inconstancies, resulting in extract 2 showing higher results than extract 1, lead to the assumption that an error may have occurred during the sampling. The decision was taken to rerun the test for the first batch. The results from the rerun is shown in the results from cylinder IDs 1A, 2A and 3A.

NOTE 4 As there was enough gas left in the cylinders, they did not need refilling between sampling. This confirms that the same gas was used for analysis for the second set of tests

.

**Table 5—Elemental impurity Vanadium**

| Elemental Impurity – Vanadium (PDE 1 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample cylinder ID | Extract 1 certified result (µg/day) | Extract 2 certified result (µg/day) | Extract 1 measured result (µg/day) | Extract 2 measured result (µg/day) | Total extract measured result (µg/day) | Total extract certified result (µg/day) | 30% PDE (µg/day) | DL (µg/day) | QL (µg/day) |
| 1 | <0,15 | <0,15 | 0,002 | 0,002 | 0,004 | <0,30 | 0,30 | 0,0004 | 0, 15 |
| 1A | <0,14 | <0,14 | 0,000 | 0,000 | 0,000 | <0,28 | 0,30 | 0,0062 | 0,14 |
| 2 | <0,15 | <0,15 | 0,002 | 0,001 | 0,003 | < 0,30 | 0,30 | 0,0004 | 0,15 |
| 2A | <0,15 | <0,15 | 0,001 | 0,002 | 0,003 | <0,30 | 0,30 | 0,0065 | 0,15 |
| 3 | <0,15 | <0,15 | 0,005 | 0,009 | 0,014 | <0,30 | 0,30 | 0,0004 | 0, 15 |
| 3A | <0,15 | <0,15 | 0,010 | 0,012 | 0,022 | <0,30 | 0,30 | 0,0066 | 0,15 |
| 4 | <0,15 | <0,15 | 0,012 | 0,013 | 0,025 | <0,30 | 0,30 | 0,0042 | 0,15 |
| 5 | <0,14 | <0,14 | 0,006 | 0,006 | 0,012 | <0,28 | 0,30 | 0,0008 | 0,14 |
| 6 | <0,14 | <0,14 | 0,022 | 0,004 | 0,026 | <0,28 | 0,30 | 0,0008 | 0,14 |
| 7 | <0,15 | <0,15 | 0,005 | -0,001 | 0,005 | <0,30 | 0,30 | 0,0012 | 0,15 |
| 8 | <0,14 | <0,14 | 0,002 | -0,001 | 0,002 | <0,28 | 0,30 | 0,0011 | 0,14 |
| 9 | <0,13 | <0,13 | 0,003 | 0,001 | 0,004 | <0,26 | 0,30 | 0,0010 | 0,13 |
| 10 | <0,15 | <0,15 | 0,004 | 0,002 | 0,06 | <0,30 | 0,30 | 0,0011 | 0,15 |
| 11 | <0,14 | <0,14 | 0,003 | 0,004 | 0,007 | <0,28 | 0,30 | 0,0011 | 0,14 |
| 12 | <0,14 | <0,14 | -0,001 | -0,007 | 0,000 | <0,28 | 0,30 | 0,0011 | 0,14 |
| 13 | <0,14 | <0,14 | -0,002 | -0,002 | 0,000 | <0,28 | 0,30 | 0,0019 | 0,14 |
| 14 | <0,14 | <0,14 | 0,002 | 0,002 | 0,004 | <0,27 | 0,30 | 0,0019 | 0,14 |
| 15 | <0,15 | <0,15 | 0,004 | 0,006 | 0,010 | <0,30 | 0,30 | 0,0020 | 0,15 |
| 16 | <0,15 | <0,15 | 0,006 | 0,019 | 0,025 | <0,30 | 0,30 | 0,0051 | 0,15 |
| 17 | <0,15 | <0,15 | 0,021 | 0,028 | 0,049 | <0,30 | 0,30 | 0,0051 | 0,15 |
| 18 | <0,14 | <0,14 | 0,042 | 0,041 | 0,083 | <0,28 | 0,30 | 0,0049 | 0,15 |

NOTE: Negative extract values are caused by background noise due to the presence of trace amounts of the element in the blank standard. These values are assumed to be zero in the interpretation of the results.

### Table 6—Elemental impurity - Chromium

| Elemental Impurity – Chromium (PDE3 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | DL (µg/day) | QL (µg/day) |
| 1 | <0,15 | <0,15 | 0,031 | 0,045 | 0,076 | <0,32 | 0,90 | 0,0057 | 0,16 |
| 1A | <0,14 | <0,14 | 0,020 | 0,047 | 0,067 | <0,28 | 0,90 | 0,0030 | 0,14 |
| 2 | <0,15 | <0,15 | 0,050 | 0,045 | 0,095 | < 0,30 | 0,90 | 0,0059 | 0,15 |
| 2A | <0,15 | <0,15 | 0,036 | 0,078 | 0,114 | <0,30 | 0,90 | 0,0032 | 0,15 |
| 3 | <0,16 | <0,16 | -0,003 | 0,095 | 0,095 | <0,33 | 0,90 | 0,0063 | 0,17 |
| 3A | <0,15 | <0,15 | 0,036 | 0,078 | 0,114 | <0,30 | 0,90 | 0,0032 | 0,15 |
| 4 | <0,15 | <0,15 | 0,041 | 0,048 | 0,089 | <0,29 | 0,90 | 0,0052 | 0,15 |
| 5 | <0,14 | <0,14 | 0,019 | 0,041 | 0,060 | <0,28 | 0,90 | 0,0233 | 0,14 |
| 6 | 0,33 | <0,14 | 0,328 | 0,064 | 0,392 | 0,47 | 0,90 | 0,0238 | 0,14 |
| 7 | <0,15 | <0,15 | 0,073 | 0,067 | 0,140 | <0,30 | 0,90 | 0,0015 | 0,15 |
| 8 | <0,24 | <0,24 | 0,054 | 0,045 | 0,099 | <0,48 | 0,90 | 0,0015 | 0,24 |
| 9 | <0,22 | <0,22 | 0,062 | 0,043 | 0,105 | <0,44 | 0,90 | 0,0014 | 0,22 |
| 10 | <0,24 | <0,24 | 0,082 | 0,052 | 0,134 | <0,49 | 0,90 | 0,0011 | 0,24 |
| 11 | <0,24 | <0,24 | 0,027 | 0,061 | 0,088 | <0,48 | 0,90 | 0,0015 | 0,24 |
| 12 | <0,24 | <0,24 | 0,041 | 0,046 | 0,087 | <0,47 | 0,90 | 0,0015 | 0,24 |
| 13 | <0,14 | <0,14 | 0,036 | 0,028 | 0,064 | <0,28 | 0,90 | 0,0109 | 0,14 |
| 14 | <0,14 | <0,14 | 0,002 | 0,002 | 0,004 | <0,28 | 0,90 | 0,0109 | 0,14 |
| 15 | <0,15 | <0,15 | 0,043 | 0,054 | 0,097 | <0,30 | 0,90 | 0,0118 | 0,15 |
| 16 | <0,15 | <0,15 | 0,031 | 0,051 | 0,082 | <0,30 | 0,90 | 0,0071 | 0,15 |
| 17 | <0,15 | <0,15 | 0,036 | 0,041 | 0,078 | <0,29 | 0,90 | 0,0070 | 0,15 |
| 18 | <0,14 | <0,14 | 0,041 | 0,051 | 0,092 | <0,28 | 0,90 | 0,0069 | 0,15 |

### Table 7— Elemental impurity - Nickel

| Elemental Impurity – Nickel (PDE 5 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total Extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | DL (µg/day) | QL (µg/day) |
| 1 | <0,35 | <0,35 | 0,019 | 0,073 | 0,092 | <0,70 | 1,50 | 0,0349 | 0,35 |
| 1A | <0,24 | <0,24 | 0,062 | 0,086 | 0,148 | <0,48 | 1,50 | 0,0059 | 0,24 |
| 2 | 0,46 | <0,33 | 0,462 | 0,137 | 0,599 | <0,79 | 1,50 | 0,0149 | 0,33 |
| 2A | <0,25 | <0,25 | 0,067 | 0,040 | 0,107 | <0,50 | 1,50 | 0,0061 | 0,25 |
| 3 | 0,51 | 1,57 | 0,514 | 1,572 | 2,086 | 2,08 | 1,50 | 0,0387 | 0,35 |
| 3A | <0,26 | <0,26 | 0,147 | 0,042 | 0,189 | <0,52 | 1,50 | 0,0063 | 0,26 |
| 4 | <0,17 | <0,17 | 0,041 | 0,016 | 0,057 | <0,34 | 1,50 | 0,0072 | 0,17 |
| 5 | 0,39 | 0,25 | 0,394 | 0,249 | 0,643 | 0,64 | 1,50 | 0,0616 | 0,16 |
| 6 | 0,41 | 0,27 | 0,405 | 0,273 | 0,678 | 0,68 | 1,50 | 0,0315 | 0,17 |
| 7 | <0,15 | <0,15 | 0,000 | 0,000 | 0,000 | <0,30 | 1,50 | 0,0190 | 0,15 |
| 8 | <0,14 | <0,14 | 0,000 | 0,000 | 0,000 | <0,28 | 1,50 | 0,0182 | 0,14 |
| 9 | <0,13 | <0,13 | 0,000 | 0,000 | 0,000 | <0,26 | 1,50 | 0,0168 | 0,13 |
| 10 | <0,15 | <0,15 | 0,031 | 0,000 | 0,031 | <0,30 | 1,50 | 0,0185 | 0,15 |
| 11 | <0,14 | <0,14 | 0,000 | 0,000 | 0,000 | <0,28 | 1,50 | 0,0181 | 0,14 |
| 12 | <0,14 | <0,14 | 0,000 | 0,006 | 0,006 | <0,28 | 1,50 | 0,0179 | 0,14 |
| 13 | <0,14 | <0,14 | 0,008 | -0,006 | 0,008 | <0,28 | 1,50 | 0,0008 | 0,14 |
| 14 | <0,14 | <0,14 | 0,017 | 0,012 | 0,039 | <0,28 | 1,50 | 0,0008 | 0,14 |
| 15 | <0,15 | <0,15 | 0,005 | 0,012 | 0,017 | <0,30 | 1,50 | 0,0008 | 0,15 |
| 16 | <0,15 | <0,15 | 0,025 | 0,106 | 0,131 | <0,30 | 1,50 | 0,0052 | 0,15 |
| 17 | <0,15 | <0,15 | 0,064 | 0,027 | 0,091 | <0,30 | 1,50 | 0,0052 | 0,15 |
| 18 | <0,15 | <0,15 | 0,067 | 0,028 | 0,095 | <0,30 | 1,50 | 0,0051 | 0,15 |

**Table 8—Elemental impurity - Copper**

| Elemental Impurity – Copper (PDE 30 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total Extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | DL (µg/day) | QL (µg/day) |
| 1 | <0,16 | <0,16 | 0,112 | 0,062 | 0,174 | <0,32 | 9,00 | 0,0030 | 0,16 |
| 1A | <0,14 | <0,14 | 0,076 | 0,027 | 0,103 | <0,28 | 9,00 | 0,0070 | 0,14 |
| 2 | <0,15 | <0,15 | 0,104 | 0,102 | 0,206 | <0,30 | 9,00 | 0,0022 | 0,15 |
| 2A | <0,15 | <0,15 | 0,044 | 0,037 | 0,081 | <0,30 | 9,00 | 0,0074 | 0,15 |
| 3 | 1,01 | 1,46 | 1,006 | 1,462 | 2,468 | 2,47 | 9,00 | 0,0034 | 0,16 |
| 3A | <0,15 | <0,15 | 0,085 | 0,027 | 0,112 | <0,30 | 9,00 | 0,0075 | 0,15 |
| 4 | <0,20 | <0,20 | 0,048 | 0,032 | 0,070 | <0,40 | 9,00 | 0,0049 | 0,20 |
| 5 | 0,25 | 0,24 | 0,250 | 0,241 | 0,491 | 0,49 | 9,00 | 0,0084 | 0,19 |
| 6 | 0,35 | <0,19 | 0,353 | 0,044 | 0,397 | <0,54 | 9,00 | 0,0086 | 0,19 |
| 7 | <0,15 | <0,15 | -0,023 | -0,105 | 0,000 | <0,30 | 9,00 | 0,1058 | 0,15 |
| 8 | <0,15 | <0,15 | -0,080 | -0,143 | 0,000 | <0,30 | 9,00 | 0,1009 | 0,15 |
| 9 | <0,14 | <0,14 | -0,022 | -0,103 | 0000 | <0,28 | 9,00 | 0,0936 | 0,14 |
| 10 | <0,15 | <0,15 | -0,027 | 0,034 | 0,034 | <0,30 | 9,00 | 0,1033 | 0,15 |
| 11 | <0,15 | <0,15 | 0,068 | 0,023 | 0,091 | <0,30 | 9,00 | 0,1007 | 0,15 |
| 12 | <0,15 | <0,15 | -0,148 | -0,255 | 0,000 | <0,30 | 9,00 | 0,0995 | 0,15 |
| 13 | <0,14 | <0,14 | -0,002 | -0,002 | 0,000 | <0,28 | 9,00 | 0,0098 | 0,14 |
| 14 | 0,19 | <0,14 | 0,187 | 0,043 | 0,230 | <0,33 | 9,00 | 0,0098 | 0,14 |
| 15 | <0,15 | <0,15 | 0,080 | 0,000 | 0,080 | <0,30 | 9,00 | 0,0107 | 0,15 |
| 16 | <0,16 | 0,30 | 0,070 | 0,300 | 0,370 | <0,46 | 9,00 | 0,0036 | 0,16 |
| 17 | 0,16 | <0,16 | 0,161 | 0,063 | 0,224 | <0,32 | 9,00 | 0,0036 | 0,16 |
| 18 | 0,30 | <0,15 | 0,297 | 0,062 | 0,359 | <0,45 | 9,00 | 0,0035 | 0,15 |

**Table 9—Elemental impurity - Molybdenum**

| Elemental Impurity – Molybdenum (PDE 10 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total Extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | DL (µ/litre) | QL (µg/day) |
| 1 | <0,16 | <0,16 | 0,007 | 0,003 | 0,019 | <0,32 | 3,00 | 0,0080 | 0,16 |
| 1A | <0,14 | <0,14 | 0,026 | 0,029 | 0,055 | <0,28 | 3,00 | 0,0064 | 0,14 |
| 2 | <0,15 | <0,15 | 0,003 | 0,003 | 0,006 | <0,30 | 3,00 | 0,0018 | 0,15 |
| 2A | <0,15 | <0,15 | 0,010 | 0,002 | 0,012 | <0,30 | 3,00 | 0,0066 | 0,15 |
| 3 | <0,16 | <0,16 | -0,007 | 0,007 | 0,007 | <0,32 | 3,00 | 0,0089 | 0,16 |
| 3A | <0,15 | <0,15 | 0,010 | 0,002 | 0,012 | <0,30 | 3,00 | 0,0068 | 0,15 |
| 4 | <0,15 | <0,15 | 0,028 | 0,006 | 0,034 | <0,30 | 3,00 | 0,0022 | 0,15 |
| 5 | <0,14 | <0,14 | 0,009 | 0,007 | 0,016 | <0,28 | 3,00 | 0,0009 | 0,14 |
| 6 | <0,14 | <0,14 | 0,057 | 0,005 | 0,062 | <0,28 | 3,00 | 0,0009 | 0,14 |
| 7 | <0,15 | <0,15 | 0,005 | 0,002 | 0,007 | <0,30 | 3,00 | 0,0019 | 0,15 |
| 8 | <0,14 | <0,14 | 0,007 | 0,002 | 0,009 | <0,28 | 3,00 | 0,0018 | 0,14 |
| 9 | <0,13 | <0,13 | 0,008 | 0,001 | 0,009 | <0,26 | 3,00 | 0,0017 | 0,13 |
| 10 | <0,15 | <0,15 | 0,008 | 0,006 | 0,014 | <0,30 | 3,00 | 0,0019 | 0,15 |
| 11 | <0,14 | <0,14 | 0,007 | 0,002 | 0,009 | <0,28 | 3,00 | 0,0018 | 0,14 |
| 12 | <0,14 | <0,14 | 0,008 | 0,005 | 0,013 | <0,28 | 3,00 | 0,0018 | 0,14 |
| 13 | <0,14 | <0,14 | -0,001 | 0,003 | 0,003 | <0,28 | 3,00 | 0,0079 | 0,14 |
| 14 | <0,14 | <0,14 | 0,000 | -0,001 | 0,000 | <0,28 | 3,00 | 0,0079 | 0,14 |
| 15 | <0,15 | <0,15 | 0,001 | -0,001 | 0,001 | <0,30 | 3,00 | 0,0085 | 0,15 |
| 16 | <0,15 | <0,15 | 0,003 | 0,003 | 0,006 | <0,30 | 3,00 | 0,0042 | 0,15 |
| 17 | <0,15 | <0,15 | 0,002 | 0,003 | 0,005 | <0,30 | 3,00 | 0,0042 | 0,15 |
| 18 | <0,14 | <0,14 | 0,002 | 0,002 | 0,004 | <0,28 | 3,00 | 0,0041 | 0,14 |

**Table 10—Elemental impurity - Tin (PDE 60 µg/day)**

| Elemental Impurity – Tin | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total Extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | Detection Limit (µg/day) | Quant. Limit (µg/day) |
| 1 | <0,16 | <0,16 | 0,071 | 0,011 | 0,082 | <0,32 | 18,0 | 0,0035 | 0,16 |
| 1A | <0,15 | <0,15 | 0,010 | 0,002 | 0,012 | <0,30 | 18,0 | 0,0023 | 0,15 |
| 2 | <0,15 | <0,15 | 0,047 | 0,025 | 0,072 | <0,30 | 18,0 | 0,0036 | 0,15 |
| 2A | <0,15 | <0,15 | 0,027 | 0,033 | 0,060 | <0,30 | 18,0 | 0,0024 | 0,15 |
| 3 | 0,20 | <0,16 | 0,196 | 0,041 | 0,237 | <0,36 | 18,0 | 0,0039 | 0,16 |
| 3A | <0,15 | <0,15 | 0,051 | 0,050 | 0,101 | <0,30 | 18,0 | 0,0024 | 0,15 |
| 4 | <0,15 | <0,15 | 0,007 | 0,000 | 0,007 | <0,30 | 18,0 | 0,0016 | 0,15 |
| 5 | <0,14 | <0,14 | 0,024 | 0,024 | 0,048 | <0,28 | 18,0 | 0,0148 | 0,14 |
| 6 | <0,14 | <0,14 | 0,021 | -0,013 | 0,021 | <0,28 | 18,0 | 0,0151 | 0,14 |
| 7 | <1,49 | <1,49 | -0,377 | -0,419 | 0,000 | <2,98 | 18,0 | 0,0010 | 1,49 |
| 8 | <1,42 | <1,42 | -0,388 | -0,402 | 0,000 | <2,84 | 18,0 | 0,0010 | 1,42 |
| 9 | <1,32 | <1,32 | -0,325 | -0,372 | 0,000 | <2,64 | 18,0 | 0,0009 | 1,32 |
| 10 | <1,46 | <1,46 | -0,380 | 0,000 | 0,000 | <2,92 | 18,0 | 0,0010 | 1,46 |
| 11 | <1,42 | <1,42 | 0,000 | 0,000 | 0,000 | <2,84 | 18,0 | 0,0010 | 1,42 |
| 12 | <1,41 | <1,41 | -0,412 | -0,483 | 0,000 | <2,82 | 18,0 | 0,0010 | 1,41 |
| 13 | <0,14 | <0,14 | -0,029 | -0,032 | 0,000 | <0,28 | 18,0 | 0,0056 | 0,14 |
| 14 | <0,14 | <0,14 | -0,014 | -0,012 | 0,000 | <0,28 | 18,0 | 0,0056 | 0,14 |
| 15 | <0,15 | <0,15 | -0,007 | -0,004 | -0,011 | <0,30 | 18,0 | 0,0060 | 0,15 |
| 16 | <0,15 | <0,15 | -0,034 | -0,028 | 0,000 | <0,30 | 18,0 | 0,0342 | 0,15 |
| 17 | <0,15 | <0,15 | -0,030 | -0,026 | 0,000 | <0,30 | 18,0 | 0,0341 | 0,15 |
| 18 | <0,14 | <0,14 | -0,023 | -0,012 | 0,000 | <0,28 | 18,0 | 0,0333 | 0,14 |

**Table 11—Elemental impurity - Lead**

| Elemental Impurity – Lead (PDE 5 µg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample Cylinder ID | Extract 1 Certified Result (µg/day) | Extract 2 Certified Result (µg/day) | Extract 1 Measured Result (µg/day) | Extract 2 Measured Result (µg/day) | Total Extract Measured Result (µg/day) | Total Extract Certified Result (µg/day) | 30% PDE (µg/day) | DL (µ/litre) | QL (µg/day) |
| 1 | <0,16 | <0,16 | 0,080 | 0,038 | 0,116 | <0,32 | 1,50 | 0,0022 | 0,16 |
| 1A | 0,17 | <0,14 | 0,174 | 0,069 | 0,17 | <0,31 | 1,50 | 0,0005 | 0,14 |
| 2 | <0,15 | <0,15 | 0,082 | 0,055 | 0,137 | <0,30 | 1,50 | 0,0008 | 0,15 |
| 2A | <0,15 | <0,15 | 0,071 | 0,059 | 0,130 | <0,30 | 1,50 | 0,0005 | 0,15 |
| 3 | 0,57 | 0,91 | 0,574 | 0,907 | 1,481 | 1,48 | 1,50 | 0,0025 | 0,16 |
| 3A | 0,18 | <0,15 | 0,184 | 0,084 | 0,268 | <0,32 | 1,50 | 0,0005 | 0,15 |
| 4 | <0,15 | <0,15 | 0,066 | 0,014 | 0,080 | <0,30 | 1,50 | 0,0011 | 0,15 |
| 5 | 0,27 | 0,40 | 0,268 | 0,404 | 0,672 | 0,67 | 1,50 | 0,0044 | 0,14 |
| 6 | <0,15 | <0,15 | 0,082 | 0,024 | 0,106 | <0,30 | 1,50 | 0,0045 | 0,15 |
| 7 | <0,15 | <0,15 | 0,050 | 0,025 | 0,075 | <0,30 | 1,50 | 0,0019 | 0,15 |
| 8 | <0,14 | <0,14 | 0,020 | 0,024 | 0,044 | <0,28 | 1,50 | 0,0018 | 0,14 |
| 9 | <0,13 | <0,13 | 0,040 | 0,016 | 0,056 | <0,26 | 1,50 | 0,0017 | 0,13 |
| 10 | <0,15 | <0,15 | 0,046 | 0,036 | 0,082 | <0,30 | 1,50 | 0,0018 | 0,15 |
| 11 | <0,14 | <0,14 | 0,022 | 0,026 | 0,048 | <0,28 | 1,50 | 0,0018 | 0,14 |
| 12 | <0,14 | <0,14 | 0,014 | 0,023 | 0,037 | <0,28 | 1,50 | 0,0018 | 0,14 |
| 13 | <0,14 | <0,14 | 0,013 | 0,007 | 0,020 | <0,28 | 1,50 | 0,0009 | 0,14 |
| 14 | <0,14 | <0,14 | 0,010 | 0,009 | 0,019 | <0,28 | 1,50 | 0,0009 | 0,14 |
| 15 | <0,15 | <0,15 | 0,007 | 0,006 | 0,013 | <0,30 | 1,50 | 0,0010 | 0,15 |
| 16 | <0,15 | <0,15 | 0,013 | 0,017 | 0,030 | <0,30 | 1,50 | 0,0020 | 0,15 |
| 17 | <0,15 | <0,15 | 0,016 | 0,020 | 0,036 | <0,30 | 1,50 | 0,0020 | 0,15 |
| 18 | <0,14 | <0,14 | 0,016 | 0,020 | 0,036 | <0,30 | 1,50 | 0,0019 | 0,14 |

## 7 Assessment and conclusion

The analytical results confirm that identified EIs are below their respective 30% PDEs levels, based on a sampling volume defined by the maximum delivered dosage.

The risk assessment identified that lead, vanadium, nickel, molybdenum, copper, tin and chromium are the only identified elements from those specified in ICH Q3D, as being present. These elements can only be derived from the manufacturing equipment or the CCSs.

**Table 12—Summary of elemental impurity data for potential components**

| Element | No. of cylinders tested | PDE (µg/day) | 30% PDE (µg/day) | **Maximum measured results (µg/day) | ***Maximum certified results (µg/day) |
|---|---|---|---|---|---|
| Lead (Pb) | 18 | 5 | 1,5 | 0,672 | 0,67 |
| Vanadium (V)* | 18 | 1 | 0,3 | 0,083 | <0,3 |
| Nickel (Ni) | 18 | 5 | 1,5 | 0,678 | 0,68 |
| Molybdenum (Mo) | 18 | 10 | 3 | 0,062 | <0,3 |
| Copper (Cu) | 18 | 30 | 9 | 0,491 | <0,54 |
| Tin (Sn) | 18 | 60 | 18 | 0,101 | <2,98 |
| Chromium (Cr) | 18 | 3 | 0,9 | 0,392 | <0,49 |

*NOTE—The tests were initially designed to demonstrate that the results are below the PDE and not the 30% limit of the PDE. It was decided not to repeat the tests with the lower QL as the results showed that the EI were below the ICH Q3D limits, especially taken into account that the measured results for the vanadium were close or even below the DL.

**NOTE—The maximum measured result is the maximum of the total extract measured result which is the sum of the two extracts 1 and 2

***NOTE—The maximum certified result is the maximum of the total extract certified result, which is either twice the quantification limit or the actual measured value whichever is the greatest.

The risk assessment carried out prior to carrying out the testing for EIs in medicinal gases has shown that there are potentially only seven elements that could be present in the gases. These impurities relate to elements that are either potentially present in the manufacturing equipment and/or in the containers closure systems used to distribute the gases.

The results indicate that the elements identified in the risk assessment are present at levels below the 30% limit of the respective PDEs, specified in the ICH Q3D requirements.

From this publication, it is concluded that the results can be applied to all medicinal gases supplied by the EIGA, CGA, JIMGA, and AIGA member companies that are approved or covered by marketing authorisations, including:

- oxygen;
- air, synthetic;
- air, compressed;
- carbon dioxide;
- nitrous oxide;
- nitrogen;

- xenon;
- helium;
- argon;
- nitrous oxide/oxygen mixtures;
- nitric oxide in nitrogen;
- helium/oxygen mixtures;
- carbon dioxide/oxygen mixtures; and
- Methane/acetylene/carbon monoxide and oxygen in nitrogen, referred to as lung function mixtures.
- Argon/oxygen mixtures;

For all of these medicinal gases:

- The medicinal gas packages use the same type of CCSs and manufacturing equipment; and
- The risks associated for these medicinal gas manufacturing processes are at least as low as those identified for the manufacturing process used for medical oxygen.

In coming to the conclusion that EI risks associated with medicinal oxygen supplied in cylinders fitted with valves with integrated pressure regulator was the worst-case scenario, it can be demonstrated that a very conservative approach has been taken. Under most situations, the MDDs for medicinal oxygen is significantly less than the 10,800 litres per day that was taken for these measurements.

It can also be concluded that all other medicinal gases will be well within the ICH Q3D limits and not require any specific ongoing testing for EIs.

These results demonstrate that the established manufacturing and supply systems are in control and ensure that the levels of potential EIs in all medicinal gases are maintained well below their 30% limit of the respective PDEs.

This demonstrates there are no additional risks, leaving the benefit risk ratio of all medicinal gases as positive.

This publication may be used by companies as a reference document when preparing their assessment for EIs with all medicinal gases approved or covered by marketing authorisations. Where the gas companies use different process or equipment to those described in this document, they will need to review their risk assessment, and its conclusions, using this document as a reference.

## 8 References

Unless otherwise specified, the latest edition shall apply.

[1] ICH Harmonised Guideline, Q3D *Guideline for Elemental Impurities*, International Conference on Harmonization. www.ich.org

[2] ISO/IEC 17025, *General Requirements for the Competence of Testing and Calibration Laboratories*. www.cen.eu

[3] European Pharmacopoeia Commission. www.edqm.eu

[4] EIGA Doc 70, *Carbon Dioxide Food and Beverages Grade, Source Qualification, Quality Standards and Verification*, European Industrial Gases Association. www.eiga.eu

[5] ISO 10524-3, *Pressure Regulators For Use With Medical Gases - Part 3: Pressure Regulators Integrated With Cylinder Valves (VIPRs)* www.cen.eu

## 9 Additional References

*United States Pharmacopeia and The National Formulary (USP–NF) General Chapter <232> Elemental Impurities – Limits*, U.S. Pharmacopeia. www.usp.org

*United States Pharmacopeia and The National Formulary, (USP–NF) General Chapter <233> Elemental Impurities – Procedure*, U.S. Pharmacopeia. www.usp.org

*Guidance for Industry: Elemental Impurities in Drug Products*, Food and Drug Administration. www.fda.gov

## Appendix A—Air separation process (covering oxygen, nitrogen, argon, air synthetic, air compressed and mixtures of these)

Air separation process does not require any catalyst or the intentional addition of substances containing EIs. An air separation plant is usually referred to as an ASU, air separation unit.

However, potential for contamination entering the process as airborne particulate or particulate released by the manufacturing equipment is taken into consideration.

EIs are present in gases mainly as particulate matter, as their vapour pressure allows excluding the presence of metal vapours and metal oxide vapours. Only mercury can be present as vapour when in the elemental state (Hg0).

The air separation processes has several steps contributing to the containment and reduction of the airborne particulate matter and of the vapours:

- A mechanical filter: ASU plants air intake filters are F6 or higher class, which allows a removal of not less than 60% of particles with a diameter of 0,4 µm and higher removal rates for larger particles;
- A wet scrubbing step, for example the spray cooler;
- Several steps where moist air is compressed, and condensed water is drained. These steps behave like a condensation filter;
- A pre-purification unit (PPU) where air is dried on absorbing beds made of alumina and molecular sieves, usually zeolites. The PPU behaves like a granular bed filter;
- After the PPU the process fluid is extremely dry. When in the cryogenic liquid phase, both oxygen and nitrogen have a very low dielectric constant. In such conditions any corrosion of the process equipment, and thus the release of particulate matter from the equipment to the process fluid, can be excluded.

Literature surveys have shown that:

- Wet scrubbing of gas streams is highly effective in removing particles. Spray towers rely primarily on particle collection by impaction; therefore, they have high collection efficiencies for coarse PM. Typical removal efficiencies for a spray tower can be as great as 90% for particles larger than 5 µm. Removal efficiencies for particles from 3 to 5 µm in diameter range from 60% to 80%. Below 3 µm, removal efficiencies decline to less than 50%.[2]
- Water condensation phenomena are effective in scavenging airborne particles. In a condensation scrubber, the particulate matter act as condensation nuclei for the formation of droplets. Collection efficiencies of greater than 99% have been reported for particulate emissions, based on study results.[3]
- Granular bed filtration is a well-established technology for the removal of particles based on inertial impact and agglomeration. Filtration efficiencies well above 90% are reported.[4, 5]

The PPU itself does not contribute to the EIs considered by the ICH Q3D guideline as the packed bed is made of alumina and zeolite 13X.

Thus, a series of process features allows excluding the presence in the bulk gas of EIs coming either from the starting materials or from the process equipment before the drying unit.

[2] EPA/452/B-02-001 *Particulate Matter Controls*
[3] EPA-452/F-03-010 *Air Pollution Control Technology Fact Sheet*
[4] Johnny Ødegård, *Gas Cleaning with Granular Bed Filter*, Norwegian University of Science and Technology, 2009
[5] EPA-600/7-79-020 *Evaluation of Granular Bed Filters for High-temperature / High-pressure Particulate Control*

From that point on, only traces of heavy elements coming from either the manufacturing equipment downstream the drying unit or from the container closure system can be considered.

The materials using for the pipelines, storage and transport vessels, as well as for the filling of cylinders are the same for all medicinal gases. Thus, the contribution of the manufacturing and container closure system is independent from the medicinal gas.

Figure 3 provides an overview of the process and of the potential for EI contamination and removal.

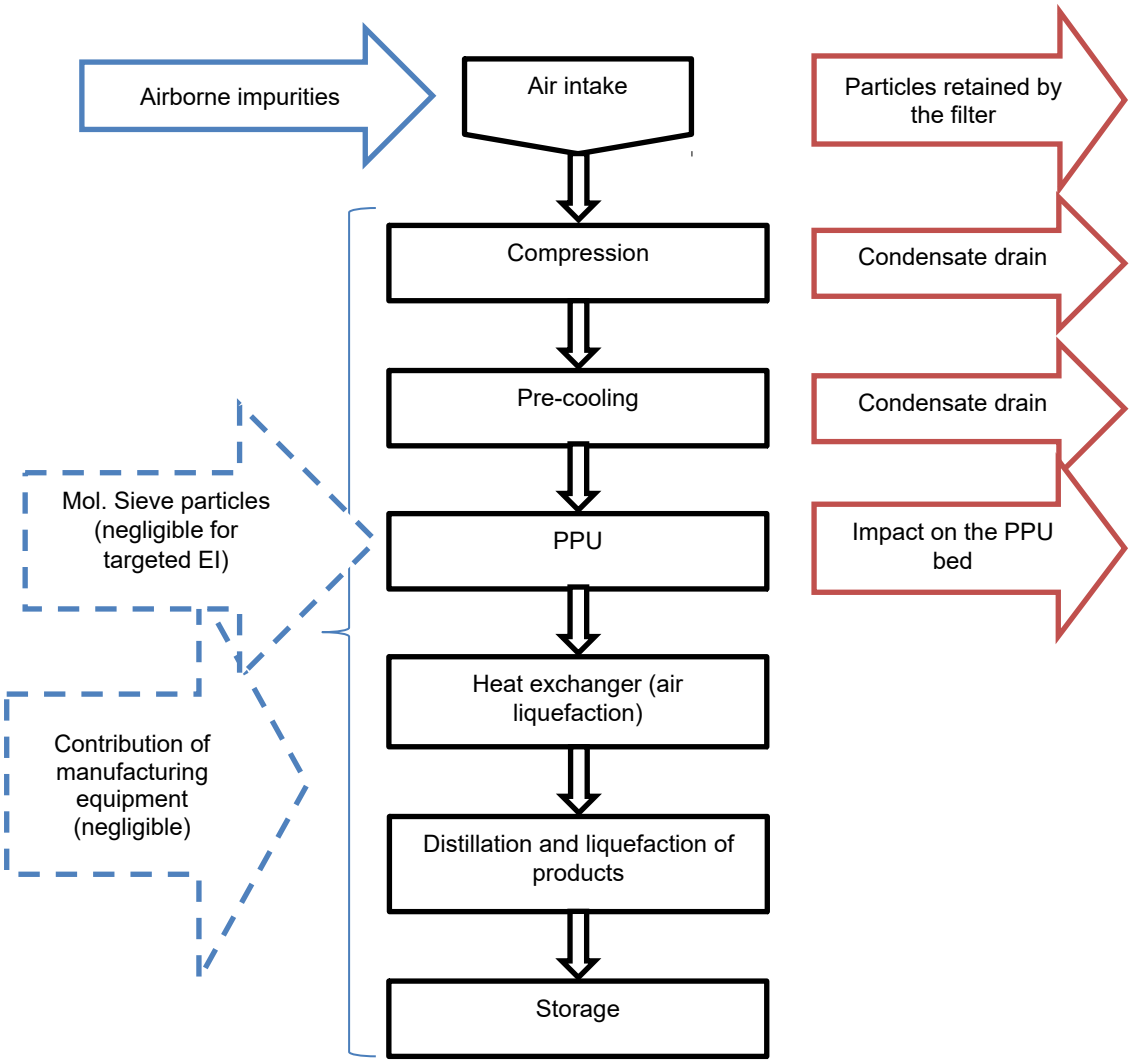



**Figure 3—Overview of the ASU process and of the potential for EI contamination and removal**

Air separation process has been addressed by two simulations to understand if EIs present as airborne particulate can concentrate:

- In oxygen at a level such that a long-term therapy would cause an intake greater than the PDE set by ICH Q3D; and
- In compressed medicinal air, when an air stream is taken from the main process immediately after the PPU and compressed into cylinders, again at a level such that a long-term therapy would cause an intake greater than the PDE set by ICH Q3D.

The main assumptions and steps undertaken are:

**1** The simulation has addressed only impurities considered relevant for the inhalation pathway;

**2** Literature has been searched for levels in air (monitored or estimated). The highest or worst-case values have been considered MAC;

**3** A reduction by 60% operated by the air intake filter, followed by a reduction by 99% operated by the condensation and water removal have been considered, after treatment concentration (ATC). To be conservative, the filter reduction factor has not been considered for mercury.

$$ATC = MAC \times 0,4 \times 0,01 \text{ (all but Hg) } ATC = MAC \times 0,01 \text{ (Hg)}$$

ATC is the concentration value used to calculate the exposure of a patient long term treated with compressed medicinal air;

**4** It has been assumed that, in a fully conservative way, all the not retained particles would concentrate in oxygen. This results in a concentration in oxygen five times greater than that in air, worst case in oxygen concentration (WCOC) = 5 x ATC;

**5** It has been assumed that 10800 litres of gaseous oxygen, respiratory air, are administered to the patient, calculating the worst-case daily dose (WCDD)

$$WCDD \text{ (oxygen)} = 10,8 \times WCOC = 10,8 \times \underline{5 \times} ATC$$

**6** The WCDD has been compared with the PDE.

The results for oxygen are provided in Table 13 below, while for air, are provided in Table 14.

**Table 13—Worst case daily dose - Oxygen**

| Impurity | PDE (µg/day) | MAC (µg/m$^3$) | ATC (µg/m$^3$) | WCOC (µg/m$^3$) | WCDD (µg/day) | WCDD/PDE | Source |
|---|---|---|---|---|---|---|---|
| Cd | 2 | 0,15 | 0,0006 | 0,003 | 0,0324 | 1,62% | "1" |
| Pb | 5 | 0,4 | 0,0016 | 0,008 | 0,0864 | 1,73% | "1" |
| As | 2 | 0,03 | 0,00012 | 0,0006 | 0,00648 | 0,33% | "1" |
| Hg | 1 | 0,02 | 0,0002 | 0,001 | 0,0108 | 1,08% | "1" |
| Co | 3 | 0,61 | 0,00244 | 0,0122 | 0,13176 | 4,39% | "1" |
| V | 1 | 0,073 | 0,000292 | 0,00146 | 0,015768 | 1,58% | "1" |
| Ni | 5 | 0,328 | 0,001312 | 0,00656 | 0,070848 | 1,42% | "1" |
| Li | 25 | 0,001 | 0,000004 | 0,00002 | 0,000216 | 0,00% | "2" |
| Sb | 20 | 0,17 | 0,00068 | 0,0034 | 0,03672 | 0,19% | "1", "3" |
| Ba | 300 | 1,5 | 0,006 | 0,03 | 0,324 | 0,11% | "1" |
| Mo | 10 | 0,03 | 0,00012 | 0,0006 | 0,00648 | 0,07% | "1" |
| Cu | 30 | 4,6 | 0,0184 | 0,092 | 0,9936 | 3,31% | "1" |
| Sn | 60 | 0,8 | 0,0032 | 0,016 | 0,1728 | 0,29% | "1" |
| Cr | 3 | 0,525 | 0,0021 | 0,0105 | 0,1134 | 3,78% | "1" |

**Table 14—Worst case daily dose – Air**

| Impurity | PDE (µg/day) | MAC (µg/m$^3$) | ATC (µg/m$^3$) | WCDD air (µg/day) | WCDD/PDE air | Note | Source |
|---|---|---|---|---|---|---|---|
| Cd | 2 | 0,15 | 0,0006 | 0,00648 | 0,33% | | "1" |
| Pb | 5 | 0,4 | 0,0016 | 0,01728 | 0,35% | | "1" |
| As | 2 | 0,03 | 0,00012 | 0,001298 | 0,07% | | "1" |
| Hg | 1 | 0,02 | 0,0002 | 0,00216 | 0,22% | | "1" |
| Co | 3 | 0,61 | 0,00244 | 0,026352 | 0,88% | | "1" |
| V | 1 | 0,073 | 0,000292 | 0,0031535 | 0,32% | | "1" |
| Ni | 5 | 0,328 | 0,001312 | 0,0141695 | 0,29% | | "1" |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Li | 25 | 0,001 | 0,000004 | 4,32E-05 | 0,00% | "***" | "2" |
| Sb | 20 | 0,17 | 0,00068 | 0,007344 | 0,04% | | "1", "3" |
| Ba | 300 | 1,5 | 0,006 | 0,0648 | 0,02% | "**" | "1" |
| Mo | 10 | 0,03 | 0,00012 | 0,001296 | 0,02% | | "1" |
| Cu | 30 | 4,6 | 0,0184 | 0,19872 | 0,66% | | "1" |
| Sn | 60 | 0,8 | 0,0032 | 0,03456 | 0,06% | | "1" |
| Cr | 3 | 0,525 | 0,0021 | 0,02268 | 0,76% | | "1" |

| | |
|---|---|
| "*" | Does not consider the very worst case (air close to mercury treating industries) |
| "**" | Considers the very worst case |
| "***" | Calculated as mean+3SD |
| "1" | Toxicological profiles of the (US) Agency for Toxic Substances and Disease Registry https://www.atsdr.cdc.gov/toxprofiles/index.asp#M |
| "2" | Cakmak et al, "Metal composition of fine particulate air pollution and acute changes in cardiorespiratory physiology" Env. Poll. 189 (2014) |
| “3” | EPA "Health Effects Notebook for Hazardous Air Pollutants" - Antimony compounds |

From the data above, being the worst-case daily dose well below 30% of the PDE, can be concluded that no monitoring is necessary.

This outcome can be extended to other mixtures of air separation gases.

The evaluation of the content of impurities in oxygen presented above, already considers that all not retained impurities are transferred to the patient, which is the worst case. Mixing gases coming from the same process cannot result in a content of impurities greater than the whole (already considered for oxygen).

# Appendix B – Nitrous oxide production process

## B.1 Starting Material

Ammonium nitrate is used as the starting material for the manufacture of nitrous oxide.

Ammonium nitrate is manufactured by the reaction between ammonia and concentrated nitric acid.

No catalysts are used in the manufacture of the ammonium nitrate.

The manufacturing plant and the storage tanks are constructed from stainless steel.

Although there is a potential for the EIs used in the manufacture of the stainless steel, it is unlikely that any particles would be present in a sufficiently high enough concentration to be a potential source of EIs in the finished product.

The ammonium nitrate is supplied to the manufacturing site as a liquid, supplied at a temperature above its crystallisation temperature.

NOTE—Dependent on the point where the plant draws off the liquid ammonium nitrate, there may be magnesium present (as the prilling agent to enable the ammonium nitrate to be crystallised to manufacture solid ammonium nitrate as a fertilizer).

## B.2 Manufacturing process

Nitrous oxide is manufactured by the thermal decomposition of ammonium nitrate.

The liquid ammonium nitrate (LAN) is supplied to the manufacturing site by tanker (as a 92% solution with purified water as the balance).

As the LAN will crystallise at temperatures around 100°C, it is stored in a heated stainless-steel storage tank.

The storage tank and associated pipework is manufactured from stainless steel and the product transferred to the nitrous oxide reactor by differential pressure. There are no pumps used in the transfer process.

The LAN is transferred to the plant reactor, where the LAN is heated by an external heater to approximately 250°C.

A catalyst (mono ammonium phosphate ($NH_4H_2PO_4$)) is added to the reactor to improve the rate of reaction in the thermal decomposition of the LAN.

The crude nitrous oxide is generated as a gas and passes up through a condenser above the reactor, where excessive ammonium nitrate is recondensed back into the reactor, making it unlikely that any catalyst is removed from the reactor.

Internal and external water deluge systems are installed to control the reaction should the exothermic reaction get out of control, but these will not introduce any EIs.

The reactor, condenser, and associated pipework are constructed from stainless steel, which could potentially introduce particulate. However, as the system is operating continuously, under a minimal positive pressure, the likelihood of the generation of any particles from the internal surfaces of the pipework system are minimal. Any particulate carried over from the regulator is likely to be removed from the gas stream in the purification system.

**Purification**

The purification system consists of a number of scrubbers, where the gas is passed up through a vessel with the scrubbing medium passing down through the vessel in the opposite direction. Each vessel is packed with ceramic raschig rings to assist the scrubbing process.

The initial tower is a water scrubber to remove any trace ammonia / ammonium nitrate, where any particulate carried over from the reactor vessel condenser would be removed. There are no other elements introduced in this scrubber.

The gas is next passed through a caustic permanganate solution which is used to remove any higher oxides (NO / $NO_2$) produced in side reactions. No other chemicals are introduced into the scrubber towers.

The final stage of the purification system is to pass the gas through additional water scrubbers, to remove and caustic permanganate carryover.

**Compression**

From the purification system, the gas is transferred to a gas holder, where it is stored prior to being compressed. The pump has a bronze impellor, which could lead to particles in the product.

The gas holder is manufactured from mild steel and uses a water seal to maintain its integrity.

As the nitrous oxide is an oxidising gas, the compressors are water lubricated.

The basic casing for the compressor is steel with the moving parts within the compressor (that are in contact with the gas) being primarily of stainless-steel construction. There is a likelihood of particles being generated in the compressor and being carried out in the high pressure gas stream. The gas ex the compressor is supersaturated with moisture from the reaction/water lubrication within the compressor. The gas is passed through a water separator, which will remove any excess water from the gas stream, having cooled the gas ex the compressor. The water removed from the gas stream will tend to remove any free particles picked up in the compressor.

The gas is then passed through an alumina drier to reduce the moisture content. A filter is used to remove any particulate caused by fluidisation of the drier beds. The drier vessels are constructed from high tensile steel, which will not contain any EIs.

The high-pressure dry gas is then passed through a liquefier system that utilises a fridge plant to reduce the temperature to the point where the gas will eventually condense and be passed into storage.

**Cylinder filling**

Nitrous oxide is filled into cylinders using a standard cryogenic liquid type positive displacement pump, manufactured from stainless steel. The high-pressure filling lines the same as used for other high-pressure gas cylinder filling systems. As nitrous oxide is a liquefiable gas and filled into cylinders as a liquid at its vapour pressure, cylinders are filled individually on a scale by weight. However, this process of filling cylinders individually will have no additional impact on the likelihood of any elements being introduced into the liquid.

When the nitrous oxide is administered to patients, gas is produced by boiling the liquid, which will take place at a low rate, resulting in there being very little likelihood of any particulate present in the product being transferred to the patient via the gas supply.

**Conclusion**

From the information, the only elements that potentially could be present in the gas are those related to the stainless-steel reactor and pipework. As the gas is scrubbed in the purification section of the plant, any potential carryover from the reactor is likely to be removed in the scrubbing process. Hence it is

concluded that the manufacturing process will not lead to any of the elements specified in the legislation for respiratory products being present above the levels specified.

The materials used for the storage and distribution of the product, as well as the filling of the cylinders for the supply to the healthcare facility are no different to those used for other medicinal gases. As a consequence, the risk assessment related to these processes are applicable to nitrous oxide.

As nitrous oxide is only used as a carrier gas in anaesthesia or mixed with oxygen for analgesia, the MDD is likely to be significantly lower that the volumes estimated for medical oxygen. The gas is only used for anaesthesia and pain relief and not for any long-term treatment. Hence, there is no risk that nitrous oxide would lead to the elements specified in ICH Q3D being delivered to a patient at levels above 30% of the PDE.

## Appendix C—Nitric oxide production process

This part analyses the risks during manufacturing process of nitric oxide as an active substance and the possibility of EI to be generated or added to the product.

For nitric oxide there are two possible ways of synthesis:

- Nitric oxide is produced from sulfuric acid (diluted 55%) reaction with liquid sodium nitrite. The resulting gas is counter-current injected in washing cycle containing sodium hydroxide and then into a condenser/decanter.

- Production of nitric oxide on a large-scale as a by-product in the Ostwald process for the synthesis of nitric acid from ammonia:

  $4\ NH_3 + 5\ O_2 \Longrightarrow 4\ NO + 6\ H_2O$

  $2\ NO + O_2 \Longrightarrow 2NO_2 \Longleftrightarrow N_2O_4$

  $3\ NO_2 + H_2O \Longrightarrow 2HNO_3 + NO$

  $12\ NH_3 + 21\ O_2 \Longrightarrow 8\ HNO_3 + 4\ NO + 14\ H_2O$

  About 10% ammonia by volume is mixed in air. The mixture is rapidly passed through a series of gauzes consisting of platinum (Pt), 10% rhodium (Rh) at about 850 °C and 5 atmospheres of pressure. The reaction time is about $10^{-4}$ seconds. The residence time during which the gas is in contact with the catalyst surface is restricted to about 1 ms, in order to avoid side reactions and to minimize catalyst losses. To purify the product the nitric acid is recovered using water in an absorption column. The acid is recovered as a 60 % aqueous solution at about 40 °C. The amount of nitric oxide removed from the top of the absorption column can be controlled by adding air at the bottom of the column to further oxidize some of the nitric oxide and strip out dissolved gases from the nitric acid. The nitric oxide is recovered from the tail gas of the top of the absorption column by adsorption or condensation. The nitric oxide is passed through an adsorption bed to remove the nitrogen dioxide, water and carbon dioxide. Nitric oxide is then compressed into cylinders.

In both cases these reactions occur in liquid media and potential EI brought by starting materials (Mo, Mg, Ti, Cr, Ni, Co, Cu, Zn, or Sb which limits are in ppb) will be trapped in the liquid.

The nitric oxide gas passes then through filters containing anhydrous potassium hydroxide pellets and a molecular sieve. In this last phase, solid versus gas, EI from anhydrous potassium pellets or piping/ container wall, may be extracted and taken away.

Limits of EI in potassium anhydrous are for As 0,5 mg/kg, and heavy metals 5,0 mg/kg.

In the worst-case scenario, if 5% of total heavy metal contained in columns were extracted, this would result in an amount of EI of 10 mg*. One batch of nitric oxide being 200 $m^3$, the content of EI per litre would be:

10/200000 which equals 0,000005 mg or 0,005 µg

The MDD is 4,32 L of pure nitric oxide, or 0,0216 µg, which is below any 30% of PDE for Heavy metals and As.

These calculations allow to conclude that there is no risk to get EI in the nitric oxide as active substance up 30% of the PDE, and in that respect it is not necessary to test these elements in the finished product.

*5 mg x 40 x 5% = 10 mg, corresponding of 4 columns of 10 kg, columns are changed after each batch.

## Appendix D—Carbon dioxide production process

**Carbon dioxide raw gas**

Raw gas is carbon dioxide feed gas before the carbon dioxide purification system.

According to EIGA Doc 70 - *Carbon Dioxide Food and Beverages Grade, Source Qualification, Quality Standards and Verification*, the carbon dioxide manufacturing is taking raw gas from different sources like the following[4]:

- combustion;
- wells/ geothermal;
- fermentation /bioethanol ad (purely energy crops);
- anaerobic digestion (waste);
- hydrogen or ammonia;
- phosphate rock;
- coal gasification;
- ethylene oxide;
- acid neutralization; and
- vinyl acetate.

Depending on the source type, the raw gas will be supplied to the carbon dioxide plant with some possible trace of impurities in which the manufacturer has to take care in the process, see Appendix B of EIGA Doc 70 [4].

Most of the sources are the result of chemical processes. For example, the carbon dioxide raw gas produced from a fermentation process to the manufacture of industrial alcohol is the result of a chemical reaction converting sugar such as dextrose into ethyl alcohol and carbon dioxide.

Other source is from fermentation of starch processes, where butanol, acetone, and ethanol are produced together with hydrogen and carbon dioxide. The gas effluents are easily separated with charcoal adsorbers getting hydrogen and carbon dioxide that are separated by absorption towers in counter current to a flow of water. This hydrogen after passing to a caustic tower is pure source to manufacture ammonia or methanol. The carbon dioxide is a very pure raw gas for carbon dioxide manufacturing plants.

The raw gas supplied to the manufacturing plant has a very good quality, but it is a warm gas at low pressure which has to be purified and transformed to be used in the gas industry. Potential for contamination entering the process as raw gas particulate or particulate released by the manufacturing equipment is taken into consideration.

EIs are present in gases mainly as particulate matter, as their vapour pressure allows excluding the presence of metal vapours and metal oxide vapours. Only mercury can be present as vapour when in the elemental state.

**Carbon dioxide manufacturing process**

The carbon dioxide purification and liquefaction processes have several steps contributing to the containment and reduction of the raw gas particulate matter and of the vapours:

- Several steps where moisture of the raw gas is cleaned by cooling and decanting to then be compressed in several steps having intermediate cooling, where condensed water is drained. These steps behave like a condensation filter.
- A washing step with drinkable water in a scrubber. At this step there are captured impurities soluble in water like alcohols, ammonia and aldehydes, as well as weight EIs. The stream is then cooled (precooling) for dehumidification.
- A filtering step with activated carbon and particulate filters. The main purpose is to remove any odour components such as $SO_2$, $SH_2$, COS as well as hydrocarbons and aromatic BTX. There

is also a contribution of the removal of oxygenates and chlorine compounds not captured in dehydrator.
The granular activated carbon filters are usually designed to remove molecules of low boiling organic solvents and odours from air and gas of sizes between 2,36 mm (93%) and 4,75 mm (90%).

The filtration grade of the particles filter is such as it is capable to retain particles of very small size (0,01 µm).

- A drying unit (dehydrator) where the stream is dried on absorbing beds made of alumina and molecular sieves (zeolites). The unit behaves like a granular bed filter. The main purpose is to remove oxygenates (aldehydes and alcohols).
  Hydrocarbon feed streams to petroleum refining catalytic processes often contain oxygenated organic compounds and other trace contaminants which can cause catalyst deactivation and other process unit performance problems. The dehydrator is an activated alumina formed from aluminium hydrate with a proprietary additive. It is an excellent adsorbent for the removal of alcohols, aldehydes, ketones, ethers, and various other carboxylic acids from the liquid hydrocarbon feed streams to isomerization and alkylation processes. It is also appropriate for the removal of water and mercaptans from these feed streams.

- After drying the fluid comes to a reboiler, chillers for liquefying the product and a distillation column with the purpose of remove venting any non-condensable gases ($O_2$, $N_2$, Ar, CO, $H_2$, $CH_4$). The fluid is a purified product in liquid phase (below –20 °C). In such conditions any corrosion of the process equipment, and thus the release of particulate matter from the equipment to the process fluid, can be excluded.

Figure 4 provides an overview of the typical manufacturing process of carbon dioxide.

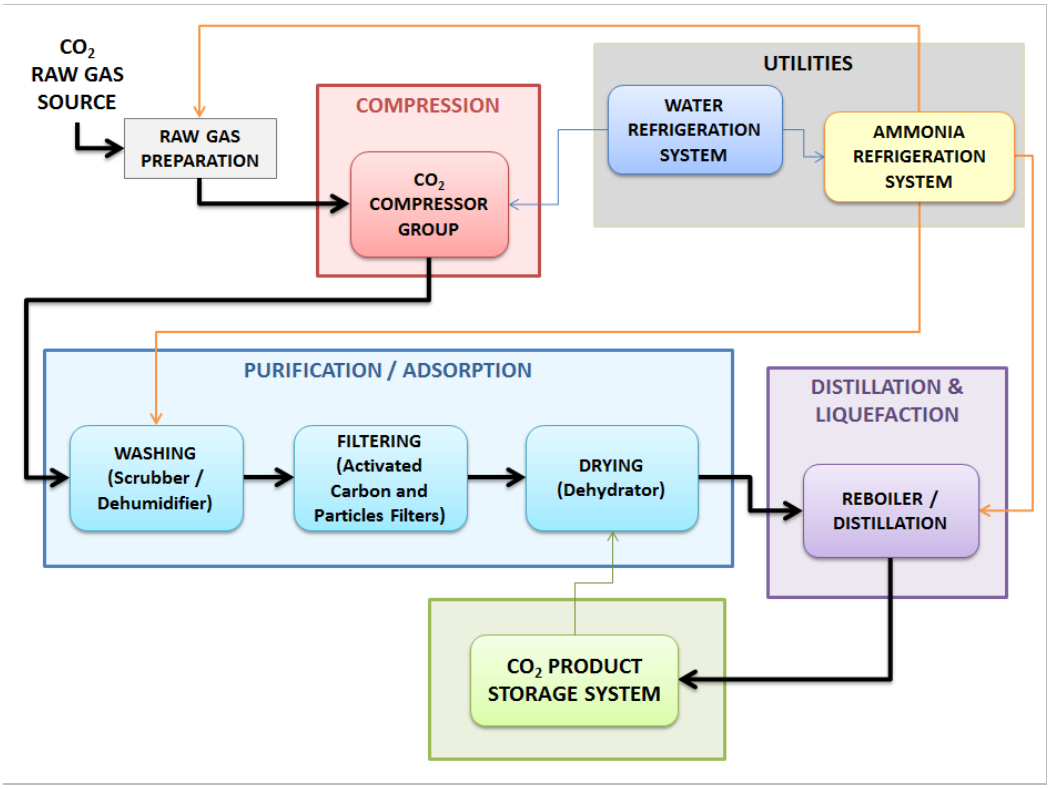



**Figure 4 - Overview of the typical manufacturing process of carbon dioxide**

Figure 5 provides an overview of the process and of the potential for EI contamination and removal.

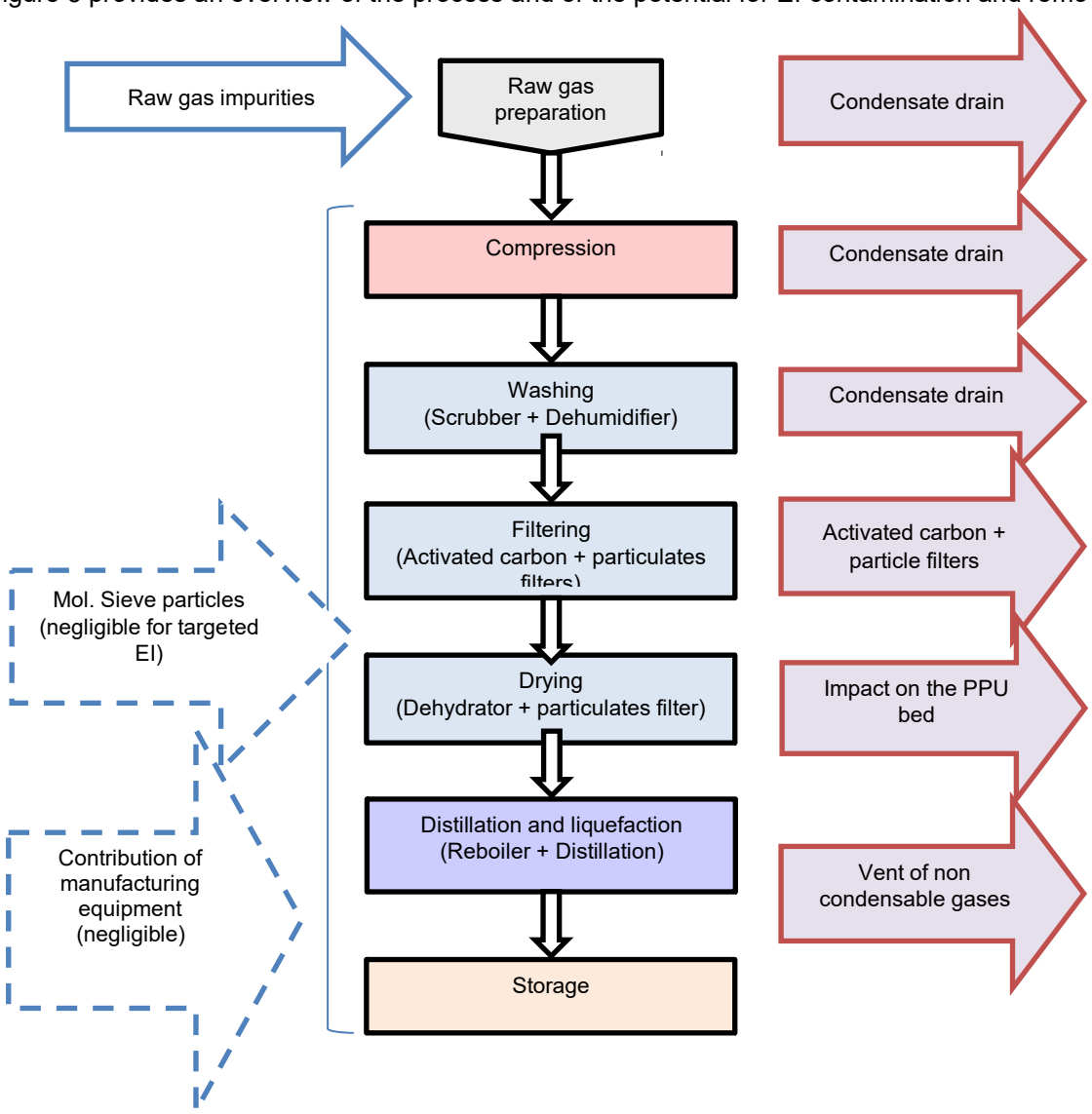



**Figure 5 - Overview of the process and of the potential for EI contamination and removal**

Literature surveys shows

- Wet scrubbing of gas streams is highly effective in removing particles. Spray towers rely primarily on particle collection by impaction; therefore, they have high collection efficiencies for coarse PM. Typical removal efficiencies for a spray tower can be as great as 90% for particles larger than 5 µm. Removal efficiencies for particles from 3 to 5 µm in diameter range from 60 to 80%. Below 3 µm, removal efficiencies decline to less than 50%;
- Water condensation phenomena are effective in scavenging particles. In a condensation scrubber, the particulate matter acts as condensation nuclei for the formation of droplets. Collection efficiencies of greater than 99% have been reported for particulate emissions, based on study results.; and
- Granular bed filtration is a well-established technology for the removal of particles based on inertial impact and agglomeration.

The drying unit itself does not contribute to the EIs considered by the ICH Q3D guideline as the packed bed is made of alumina.

Thus, a series of process features allows excluding the presence in the bulk gas of EIs coming either from the starting materials or from the process equipment before the drying unit.

From that point on, only traces of heavy elements coming from either the manufacturing equipment downstream the distillation and liquefaction.

As a summary, the water washing and condensation steps of the process, additional to the filtering process including particles filters after both the activated carbon units and dehydrator, are enough manufacturing barriers to affirm the any likelihood of a presence of EIs coming from the manufacturing process of the carbon dioxide can be excluded.

The materials used for the pipelines, storage and transport vessels, as well as for the filling of cylinders are the same for all medicinal gases. Thus, the contribution of the manufacturing and container closure system is independent from the medicinal gas.

On the other hand and added to the above considerations, the MDD of carbon dioxide is very low (22.5 litres carbon dioxide/day) which allows to conclude that there is no risk of getting EI in the carbon dioxide as an active substance up to 30% of the PDE, and in that respect it is not necessary to test these elements in the finished product.

# Appendix E – Approved Test Protocol

*Butterworth Laboratories Ltd*

**Controlled Document**

COPY FOR INFORMATION ONLY

**DOCUMENT ID: BLM640C**

**REVISION: 1**

**TITLE: Extraction of 7 Elemental Impurities from Medicinal Gas Cylinders with Integral Valves and their Determination by ICP-MS**

## INTRODUCTION

Samples of medicinal gases are discharged through two aliquots of aqueous nitric/hydrochloric acid extraction solution in Dreschel bottles. Mixed internal standard is added to extracted solutions, which are analysed by Inductively Coupled Plasma – Mass Spectrometry (ICP-MS) for the determination of the elemental impurities Lead (Pb), Vanadium (V), Nickel (Ni), Molybdenum (Mo), Copper (Cu), Tin (Sn) and Chromium (Cr).

## SCOPE

This procedure is to be applied to samples of medicinal gases, supplied in cylinders fitted with an integral pressure regulator, capable of supplying gas at a nominal flow rate of 1 L/min via a firtree connection, supplied by European Industrial Gases Association (EIGA) and/or its members; with the purpose of extracting elemental impurities into two separate aliquots of an acidic solution from a volume of gas sufficient to meet the ICH permitted daily exposure limits (below) based on the daily exposure specified by the client, with analysis by ICP-MS, compliant with the method specified in Ph. Eur. 2.4.20 Determination of Metal Catalyst or Metal Reagent Residues.

| Target Element | Class | Inhalation PDE µg/day | 30% PDE µg/day |
|---|---|---|---|
| Lead (Pb) | 1 | 5 | 1.5 |
| Vanadium (V) | 2A | 1 | 0.3 |
| Nickel (Ni) | 2A | 5 | 1.5 |
| Molybdenum (Mo) | 3 | 10 | 3 |
| Copper (Cu) | 3 | 30 | 9 |
| Tin (Sn( | 3 | 60 | 18 |
| Chromium (Cr) | 3 | 3 | 0.9 |

Note: For reporting purposes, confirmation of the current specification limits, and daily exposure volume should always be provided by the client.

## LITERATURE REFERENCES

| | |
|---|---|
| SOPIM131 series | Use of the Agilent ICP-MS systems |
| BLM498G | Determination of Trace Elements by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) in Aqueous Solution. |

## METHOD VALIDATION

Method development was performed for this sample type under Study Ref: 1706-0239.

Reference may be made to validation log no. 221 for BLM 498G as guidance to the performance of the instrument with respect to linearity, specificity, range, accuracy, precision and detection and quantitation limits; however, no formal validation procedure has been undertaken to assess the extraction procedure efficiency for gas samples.

**HEALTH AND SAFETY**

A COSHH assessment has been made on the draft method and the following safety recommendations have been made:

- Read material safety data sheets (SDS).
- When handling all reagents and sample materials, laboratory coat, gloves and safety glasses must be worn.
- Female analysts should be aware of the reproductive hazards associated with the dispensing of Cadmium, Nickel and Chromium standards.
- Dispense analytical standards within active fume hood.
- Dispense concentrated acids within active fume hood.
- Dilute standards to volume within active fume hood.
- Glassware and gas lines should be acid leached within active fume hood.
- Gas cylinders must be vertically secured with bench clamp.
- Keep gas cylinders away from sources of direct heat.
- Keep oxygen rich gases away from combustible materials, hydrocarbons and sources of ignition.
- Where gas regulator not integral to sample cylinder, a gas specific off cylinder two stage regulators must be used.
- Gas sampling Dreschel bottles must be set up in active fume hood.
- Excess gas from sampling process is to be vented within same fume hood.
- When setting up analytical instrumentation or using the computer data system, gloves should be removed.
- Neutralise acidic sample preparations before disposal.
- Analytical preparations containing Cadmium, Lead, Arsenic, Cobalt, Nickel, Silver, Chromium, Mercury and Tin must not be disposed via the water course. Preparations containing these elements should be bulk stored in suitable labelled container for disposal by registered waste contractor.

**Supervisory staff must ensure that the analyst fully understands the reactions involved before starting this operation**

**Specific Chemical Hazards:**

1) **1000 µg/mL Scandium, Yttrium, Indium, Terbium, Vanadium and Copper standards** cause skin irritation. Cause serious eye irritation - Prescribed PPE and handling controls apply.

2) **1000 µg/mL Bismuth standards** cause severe skin burns and eye damage - Prescribed PPE and handling controls apply.

3) **Nitric Acid** may intensify fire; oxidiser. Causes severe skin burns and eye damage – Keep away from combustible materials - Prescribed PPE and handling controls apply.

4) **1000 µg/mL Lead standard** may be corrosive to metals. Causes skin irritation. Causes serious eye damage. Harmful to aquatic life with long lasting effects - Avoid release to the environment - Prescribed PPE and handling controls apply.

5) **1000 µg/mL Nickel standard** causes skin irritation. May cause an allergic skin reaction. Causes serious eye irritation. May cause cancer by inhalation. May damage the unborn child. May cause damage to organs through prolonged or repeated exposure. Harmful to aquatic life with long lasting effects - Female analysts should be aware of the reproductive hazards associated with dispensing this substance - Avoid release to the environment - Prescribed PPE and handling controls apply.

6) **1000 µg/mL Molybdenum standard** may be corrosive to metals. Causes skin irritation. Causes serious eye irritation. May cause respiratory irritation - Prescribed PPE and handling controls apply.

7) **1000 µg/mL Chromium standard** causes skin irritation. May cause an allergic skin reaction. Causes serious eye irritation. May cause allergy or asthma symptoms or breathing difficulties if inhaled. May cause genetic defects. May cause cancer. May damage fertility. May damage the unborn child. Toxic to aquatic life with long lasting effects - Female analysts should be aware of the reproductive hazards associated with dispensing this substance - Avoid release to the environment - Prescribed PPE and handling controls apply.

8) **1000 µg/mL Tin standard** may be corrosive to metals. Causes severe skin burns and eye damage. May cause respiratory irritation. Harmful to aquatic life with long lasting effects - Avoid release to the environment - Prescribed PPE and handling controls apply.

9) **Hydrochloric Acid** may be corrosive to metals. Causes severe skin burns and eye damage. May cause respiratory irritation - Prescribed PPE and handling controls apply.

10) **Medical Oxygen, Medical Nitrous Oxide and Medical Gas Mixtures containing more than 25% Oxygen** are considered as oxidants and may cause or intensify fire. Medical gas cylinders contain gas under pressure; May explode if heated – Keep away from sources of heat, hydrocarbons and combustible materials - Prescribed PPE and handling controls apply.

11) **Medical Gas Cylinders (where the Oxygen content is below 25%)** contains gas under pressure; May explode if heated – Keep away from sources of heat - Prescribed PPE and handling controls apply.

**TRAINING**

Training must be carried out in accordance with SOPT2.

Trainees must demonstrate competence in performing this analysis in accordance with this method. Care must be taken to ensure that all health & safety and quality control requirements have been met, therefore close supervision should be provided at all times during training.

Training for this method requires that the analyst must have completed training in the use of the ICP-MS.

In addition the analyst must have completed training in the following procedures:

| | |
|---|---|
| SOPIM5 series | 5 figure balances |
| SOPG27 | The use of auto pipettes |
| SOPIM114 series | High purity water |
| QMP24 | QA requirements for IT systems |
| SOPG019 | The use of laboratory glassware |
| SOPIM131 series | Use of the Agilent ICP-MS systems |
| BLM498G | Determination of Trace Elements by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in Aqueous Solution |
| SOPT05 | Basic training or general inorganic analytical chemistry |
| LMP37 | Gas Cylinders and Gas Distribution Equipment |

## CHANGE CONTROL

Change control should be performed in accordance with QMP32.

This method has been developed to specifically meet the requirements of European Industrial Gases Association and as such, any proposed changes must be approved by them before putting into effect.

Any changes potentially affecting the performance characteristics of the method must be fully investigated before they take effect.

## QUALITY CONTROL

The requirements of QMP11 should be observed with regard to Quality Control requirements and actions to be taken in the result of their failure.

The RSD of each result reading of analyte and internal standard should be <5% (<10% for QL standard). The RSD requirement does not apply to blank solutions and solutions of concentration below the bottom standard. An RSD above this value indicates poor stability and is indicative of a possible problem with the instrument.

The calibration graph should be assessed for linearity and have a correlation coefficient ≥ 0.9995.

The calculated concentration for each calibration standard (with the exception of the QL standard), based on the calibration must be within 90 -110% of the expected concentration.

A standard should be prepared at the required quantitation/reporting limit. The calculated concentration, based on the calibration must be within 80 -120% of the expected concentration.

An independent QC (IQC) standard should be prepared from an alternate stock source and analysed after the calibration. Results for IQC standards must be within 90 – 110% of the expected (certified) value.

A calibration standard is run every 10 samples, and as the final sample in the sequence, to ensure excessive drift does not occur over the course of the run. Results should be between 90 – 110% of the expected value.

Internal standard is required for all analysis and is added at a concentration of 10ppb in the final solution. Internal standard recovery must be in the range 70 – 130%.

The result of the calculated concentration in solution for the Process Blank (ng/mL) multiplied by a factor of 3 and the dilution factor must be less than the Practical Quantitation Limit for the Target Element.

The sample solution preparations must be visually clear.

If any of the above QC criteria are not met, the Head of Analytical Operations must be informed, who will investigate the cause before deciding whether results can be released or further analysis is required.

**EQUIPMENT**

- Flow meter (model DM3A, or equivalent; supplied by client)
- 5 figure analytical balance
- ICP-MS, e.g. Agilent 8800 ICP-MS System, ID: BL131A, or equivalent
- Calibrated Auto pipettes
- 50 mL plastic Digitubes® with lids
- Dreschel bottles
- Gas tubing

**REAGENTS, REFERENCE MATERIALS & STANDARD PREPARATION**

Reagents

Purified water, In-house, ≥ 18MΩ.cm at source
Conc. Nitric acid, Romil-SpA™, or equivalent
Conc. Hydrochloric acid, Romil-SpA™, or equivalent
0.1N Sodium Hydroxide, Tritinorm, or equivalent

Reference Materials

Certified Scandium (Sc), Indium (In), Yttrium (Y), Terbium (Tb) and Bismuth (Bi) solutions from Romil (PrimAg®-xtra), or equivalent
Certified Lead (Pb), Vanadium (V), Nickel (Ni), Molybdenum (Mo), Copper (Cu), Tin (Sn) and Chromium (Cr ) solutions from Romil (PrimAg®-xtra), or equivalent

Standard Stocks Preparation

**Internal standard (ISTD, 1000 ng/mL Sc, Y, In, Tb and Bi):**
Pipette 0.050 mL of the 1000 µg/mL Sc, Y, In, Tb and Bi reference standards into a certified 50 mL vessel (e.g. Digitube®). Add 1 mL of conc. $HNO_3$ and make up to 50 mL with purified water.

**Standard Stock Solution 1 (1000 ng/mL Pb, V, Ni, Mo, Cu, Cr):**
Pipette 0.050 mL of the 1000 µg/mL Cd, Pb, As, Co, V, Ni, Se, Ag, Li, Ba, Mo, Cu, Cr reference standards into a 50 mL Digitube®, add 1 mL conc. $HNO_3$ and make to volume with purified water.

**Standard Stock Solution 1A (10 ng/mL Pb, V, Ni, Mo, Cu, Cr):**
Pipette 0.50 mL of Standard Stock Solution 1 into a 50 mL Digitube®, add 1 mL conc. $HNO_3$ and make to volume with purified water.

**Standard Stock Solution 2 (1000 ng/mL Sn):**
Pipette 0.050 mL of 100 µg/mL Hg, and 1000 µg/mL of Tl, Au, Pd, Ir, Os, Rh, Ru, Pt, Sb, Sn reference standards into a 50 mL Digitube®, add 10 mL conc. HCl and make to volume with purified water.

**Standard Stock Solution 2A (10 ng/mL Sn):**
Pipette 0.50 mL of Standard Stock Solution 2 into a 50 mL Digitube®, add 10 mL conc. HCl and make to volume with purified water.

Working Standards Preparation:

**Calibration Blank (to be prepared in duplicate):**
Pipette 0.50 mL of 1000 ng/mL mixed ISTD into a 50 mL Digitube®. Then add 1 mL of conc. $HNO_3$ and 0.5 mL of conc. HCl. Dilute to 50 mL with purified water.

**Standard 1 (0.1 ng/mL Pb, V, Ni, Mo, Cu, Cr, Sn):**
Pipette 0.50 mL of Standard Stock Solutions 1A and 2A into a 50 mL Digitube®, add 0.50 mL of 1000 ng/mL mixed ISTD, 1 mL of conc. $HNO_3$ and 0.5 mL of conc. HCl. Dilute to 50 mL with purified water.

**Standard 2 (1 ng/mL Pb, V, Ni, Mo, Cu, Cr, Sn):**
Pipette 0.050 mL of Standard Stock Solutions 1 and 2 into a 50 mL Digitube®, add 0.50 mL of 1000 ng/mL mixed ISTD, 1 mL of conc. $HNO_3$ and 0.5 mL of conc. HCl. Dilute to 50 mL with purified water.

**Standard 3 (10 ng/mL Pb, V, Ni, Mo, Cu, Cr, Sn):**
Pipette 0.50 mL of Standard Stock Solutions 1 and 2 into a 50 mL Digitube®, add 0.50 mL of 1000 ng/mL mixed ISTD, 1 mL of conc. $HNO_3$ and 0.5 mL of conc. HCl. Dilute to 50 mL with purified water.

**Pb, V, Ni, Mo, Cu, Cr, Sn IQC:**
A mixed standard of Pb, V, Ni, Mo, Cu, Cr, and Sn should be prepared from an independent source in the same fashion as the standards above; at a concentration within the calibration range.

Note: Alternative dilutions schemes and alternative concentrations of stock solutions may be employed provided acid and internal standard concentrations and the final elemental concentrations are maintained.

**ANALYTICAL PROCEDURE**

**1. Sample Preparation/Handling**

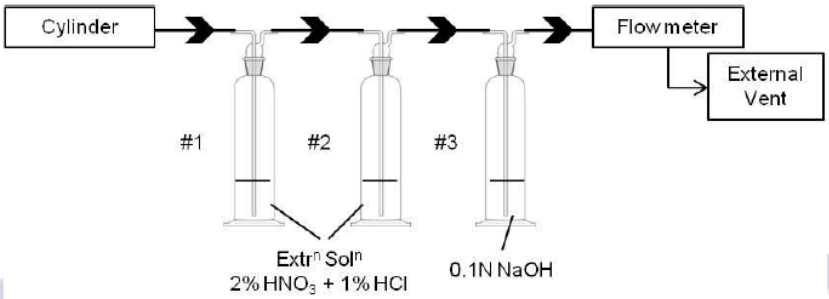
1.1 All glassware and gas lines must be leached for 12hrs in 10% v/v $HNO_3$ and 5% v/v HCl, before being thoroughly rinsed with purified water and oven dried prior to use.

1.2 Extraction Solution (2% v/v $HNO_3$; 1% v/v HCl): 20 mL conc. $HNO_3$ and 10 mL conc. HCl diluted to 1L with purified water, prepare as required.

1.3 Extraction Blank:
Add 50 mL of Extraction Solution to each 'sampling' Dreschel bottle, seal tubes with parafilm and allow to stand for a length of time not less than that required for sample extraction (*e.g.* > 8 hours for an 8 hour extraction). Then transfer to individual 50 mL Digitubes™.

1.4 Sample Extraction:
Ensure sample cylinder is adequately secured to lab bench using a cylinder bracket. Before analysis, the sample cylinder should be connected to the wet flow meter and a suitable volume of gas dispensed to allow saturation of the meter's fluid (see Appendix 1 for guidance on flow meter set-up and use).

Add 50 mL of Extraction Solution to each 'sampling' Dreschel bottle and add *c.* 50 mL 0.1N NaOH to a third Dreschel bottle. Connect the sample cylinder, 3 x Dreschel bottles and flow meter as per the diagram below, and ensure that the output from the flow meter is suitability vented to an external source or fume hood extraction:




Record the flow meter reading before sampling. Gently open cylinder until the flow selector is set to 1L/min. Sample for sufficient duration to enable reporting at ICH inhalation limits. This can be calculated based on lowest standard measured, and information provided by client stating gas exposure in L/day, for example:

$$\text{Gas sample volume required (L)} = \frac{\text{QL std (µg/mL) x Test solution volume (mL)}}{\text{0.3 x PDE (µg/day)/Exposure (L/day)}}$$

For the case of vanadium in medicinal $O_2$ with a daily dose of 21600L this gives:

$$\frac{\text{0.0001 µg/mL x 50 mL}}{\text{(0.3 x 1 µg/day / 21600L/day)}} = \text{360 L sample required}$$

At a flow rate of 1L/min this will require 360 mins = 6 h 00 min

Confirm the sampling time by monitoring flow meter rate with a laboratory stopwatch at regular intervals; the meter is calibrated as 1 rotation is equivalent to 0.25L.

1.5 Test solutions: once the required volume has been sampled according to the flow meter, shut off the cylinder and record the flow meter reading. Transfer each sampling Dreschel bottle contents to individual 50 mL Digitubes™, add 0.5 mL of mixed internal standard and make to 50 mL volume if required with purified water.

1.6 Transfer an aliquot (*e.g.* ~10 mL) of Test solution to a 15 mL polypropylene tube for presentation to the ICP-MS. Retain the remaining solution in the (capped) Digitube™ in case further analysis is required.

## 2. Instrument Procedure

2.1 Analyse the sample and standard preparations by ICP-MS in accordance with the instrument's SOP, all performance checks must be performed prior to use.

2.2 The sequence generated for running samples needs to comply with the QC requirements of this method.

2.3 An example of instrument acquisition method for target elements is shown in Appendix 2.

2.4 A typical analytical sequence is as follows:

a. Calibration Blank 1
b. Calibration Blank 2
c. Std 1
d. Std 2
e. Std 3
f. IQC std (e.g. 10 ng/mL)
g. Wash
h. Extraction Blank
i. Sample 1…10
j. Std check

2.5 Any of the calibration standards may be used as the standard check.

2.6 In the event that an overnight sequence does not meet QC requirements and samples need to be re-run, fresh dilutions or aliquots should be taken from the stock source. It is not acceptable to re-run solutions that have been standing more than 12 hours on an autosampler rack.

## CALCULATIONS

Result in µg/L = result in µg/L x volume of extraction preparation (L) / volume of gas sampled (L)

The instrument software can calculate this automatically.

Result in µg/day = result in µg/L x daily dose volume (L/day)

## REPORTING RESULTS

The results will be reported by Certificate of Analysis in table format for each extraction solution in terms of calculated daily exposure, expressed as µg/day for each analyte.

In the case where a result is determined as < the QL standard; or < 3 x the concentration of the extraction blank, then the result will be reported as < X, where X represents the QL standard (or 3 x the extraction blank) x the dilution.

The calculated QL and DL for each analyte will be reported as µg/day. The daily limit for each analyte will be presented as µg/day (ICH Q3D Step 4, Table A.2.1. Inhalation PDE, unless otherwise specified by client with sample submission).

Results should be reported to 2 significant figures.

## PERFORMANCE CHARACTERISTICS

A summary of performance characteristics obtained during validation of generic in house method BLM498G (Validation log reference 221) determined at the manufacturer's recommended isotope on an undiluted sample is presented below for guidance on instrument performance:

| | |
|---|---|
| Accuracy | Accuracy of 90-110% |
| Precision – Repeatability | NMT 10% RSD |
| Linearity & Range | Correlation coefficient r ≥ 0.9995 for all elements between QL and 100ppb. This may be extended with additional standards if required |
| Specificity | In no-gas mode, the following masses had significant interference:23(Na), 39(K), 51(V), 52(Cr), 56(Fe), 57(Fe), 75(As).<br>With the ORS gas flow set to 4ml/min satisfactory removal of interference demonstrated for all masses except 23 and 39. |
| Detection limit | Detection limits range from 0.1ppt to 10ppb |
| Quantitation Limit(QL) | The following elements have a QL of 0.1ppb or better: Li, Be, Sc, Ti, V, Cr, Mn, Co, Ni, Ga, Ge, As, Se, Rb, Sr, Y, Zr, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Sb, Te, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, Re, Ir, Pt, Au, Hg, Tl, Pb, Bi, Th, U.<br>The following elements have a QL of 1.0ppb: B, Mg Ca, Fe, Cu, Zn, W, Os<br>The following elements have a QL of 10ppb: Al, Na, P, K<br>Refer to validation results summary for isotope and gas mode used. Theoretical QL have also been provided from calibration data. |
| Robustness | Validation requirements were met with matrices containing 0.3% NaCl and 0.2% butanol. |
| Solution stability | Solutions showed good stability over 4 days with agreement of better than 95-105% for all elements except Na, K and Os. Zn also gave data outside the 95-105% range after 4 days. |
| Uncertainty of Measurement | Uncertainty of measurement is based on the allowed tolerances of QC check standards.<br>At QL 30%; Mid-range 20% |

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**APPENDIX 1**

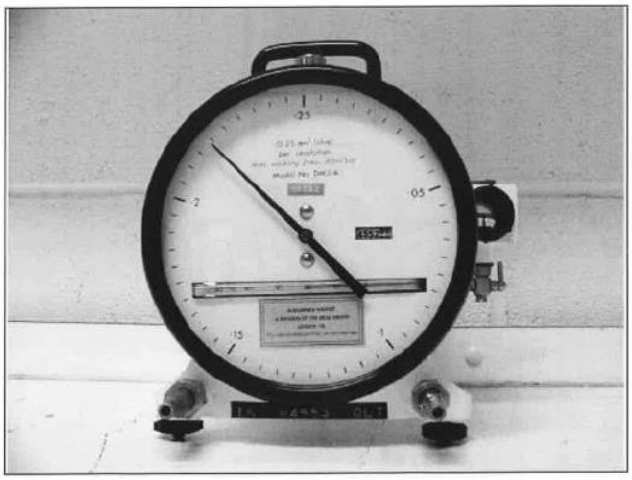
BOC

ANA-29-05-BOC
Use and Calibration of Wet Test Meters

## Use and Calibration of Wet Test Meters



**Attachment(s):**
Flow Meter Calibration Sheet



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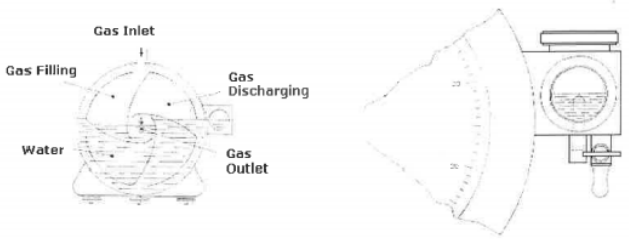
**"Hyde" type meters**

Alternatively, some instruments are constructed on the "Hyde" type principle, whereby the inlet of the meter introduces gas into the space above the water in the outer casing and the gas **must** then pass through the drum to the outlet of the meter. With this design, the height of the water in the meter is shown by an up-turned indicating point in the sight box.

Meters based on this principle of operation are capable of being calibrated to a higher degree of accuracy and are more common in BOC.

The principle of operation is shown diagrammatically as follows:




**Pressure conditions**

The wet test meters are suitable for use under pressure conditions not exceeding 4.8 kPa (49 cm wg) and should be protected by a water manometer if this condition is likely to be exceeded.

**Flow rate**

The normal flow rate for wet test meters is two revolutions of the drum per minute, which gives an accuracy of 0.25%. The meters may be used however at up to three revolutions per minute, but the accuracy will not be better than 0.5%.

**Replacing the water**

Water **must** be replaced at intervals of not more than two months. If contamination by corrosive gases occurs, then water replacement is required more frequently.

If the meter is to be stored for any length of time or be transported, it **must** be drained, flushed out with clean water and refilled when required. Purified water is preferred for filling although mains water is adequate.

**Operation process**

The general operation of the meter is as follows:

- Set up the meter.
- Carry out checks before connecting the gas supply.
- Connect the gas supply to the "inlet" ensuring that the gas from the "outlet" is vented to a safe area.
- If gases partially soluble in water, such as carbon dioxide, are being measured, a quantity **must** be passed through the meter sufficient to saturate the water before accurate measurements can be obtained.
- Record the meter reading on the analytical log sheet before any gas is passed through the instrument.
- Check that the supply pressure does not exceed 4.8 kPa (49 cm wg) and then slowly turn on the gas.
- Pass the required volume of gas through the meter and then turn off the gas supply.
- Record the final meter reading in the log sheet.
- Disconnect the equipment.

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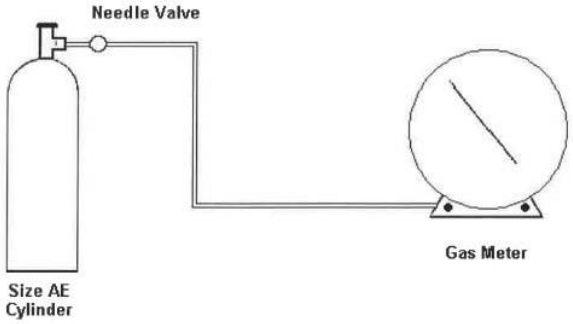
## Calibration Procedure

**Calibration intervals** Calibration of wet test meters **must** be carried out at intervals of not greater than 12 months, but more frequent calibration may be required in case of dispute over analyses or if damage to the meter is suspected. The meter may either be return to the manufacturer for calibration or calibrated in house using the following procedure.

| Step | Action | |
|---|---|---|
| 1 | In an area at constant temperature, set up the test meter and apparatus as shown below. Level the meter accurately. | ❑ |




| | | |
|---|---|---|
| 2 | Evacuate an AE size cylinder (or equivalent) and fill to full pressure with nitrogen. Allow the cylinder to cool to the laboratory ambient temperature. | ❑ |
| 3 | Weigh the cylinder using an appropriate balance of the required sensitivity and record the weight on the ***Flow Meter Calibration Sheet (see attachment)***. | ❑ |
| 4 | Using a regulator to prevent the meter being over pressurised, connect the cylinder to the gas meter and note the gas meter reading. Close the needle valve. Open the cylinder valve and using the needle valve, adjust the gas flow through the gas meter to 0.5 litres/minute. | ❑ |
| 5 | Record the meter temperature and the barometric pressure on the ***Flow Meter Calibration Sheet (see attachment)***. | ❑ |
| 6 | When approximately 50 litres of gas has been passed through the gas meter close the cylinder valve and allow the gas in the pipe to flow through the gas meter. | ❑ |
| 7 | Record the meter reading and disconnect the needle valve. | ❑ |
| 8 | Reweigh the cylinder and record the results. | |
| 9 | Check the meter temperature and barometric pressure in case of any short-term fluctuation. If there is any fluctuation, repeat the test. | |
| 10 | Repeat this procedure and calculate the mean value (see *Calculation (Page 6)*). | ❑ |

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## Recording of Results

| Step | Action | |
|---|---|---|
| 1 | Use the ***Flow Meter Calibration Sheet (see attachment)*** to calculate and record the results obtained. | ❑ |
| 2 | The mean of the two results should show a maximum meter error of 1%.<br>If the results are within this range, complete a calibrated label and attach to the meter.<br>If errors greater than 1% are found the meter **must** be withdrawn from service immediately. Attach a rejected label to the flow meter and inform the laboratory manager. | ❑ |
| 3 | File the ***Flow Meter Calibration Sheet (see attachment)*** in the appropriate instrument record file. | ❑ |

## Review of Results

**Calibration controller requirements**

The Calibration Controller **must** review calibration results to see if they are within the range of acceptable error.

The controller:

- Calculates the error and documents this on the calibration sheet
- Annotates the calibration sheet "acceptable error" or "unacceptable error" as appropriate, and
- Signs and dates the calibration sheet to show that the results have been reviewed.

Any unacceptable errors found on calibration **must** be reported to the laboratory manager.

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**APPENDIX 2**

## Acquisition Method

| | |
|---|---|
| [ACQ PARAMETERS] | |
| Data Folder | M:\2017\8800\08\1706-0239-CM-1.b\008CALS.d |
| Acq Mode | Spectrum |
| Q2 Peak Pattern | 3 points |
| Replicates | 3 |
| Sweeps/Replicate | 100 |
| | |
| Monitored Masses: | |
| Element Name | Q1 -> Q2 |
| Cd | 111 -> 111 |
| Hg | 201 -> 201 |
| Hg | 202 -> 202 |
| Tl | 205 -> 205 |
| Pb | 208 -> 208 |
| | |
| Tune Mode #1: | No Gas |
| Quick Scan | OFF |
| Independent P/A Factors | ON |
| Stabilization Time | 10 sec |
| Scan Type | Single Quad |
| Number of Masses | 18 |

| Element Name | Mass | +0.5 u | IntegTime/ Mass [sec] | Detector Mode |
|---|---|---|---|---|
| Li | 7 | OFF | 0.3 | Auto |
| Sc | 45 | OFF | 0.3 | Auto |
| Y | 89 | OFF | 0.3 | Auto |
| Ag | 107 | OFF | 0.3 | Auto |
| Cd | 111 | OFF | 3 | Auto |
| In | 115 | OFF | 0.3 | Auto |
| Sn | 118 | OFF | 0.3 | Auto |
| Sb | 121 | OFF | 0.3 | Auto |
| Ba | 137 | OFF | 0.3 | Auto |
| Tb | 159 | OFF | 0.3 | Auto |
| Os | 189 | OFF | 3 | Auto |
| Ir | 193 | OFF | 3 | Auto |
| Au | 197 | OFF | 3 | Auto |
| Hg | 201 | OFF | 3 | Auto |
| Hg | 202 | OFF | 3 | Auto |
| Tl | 205 | OFF | 0.3 | Auto |
| Pb | 208 | OFF | 0.3 | Auto |
| Bi | 209 | OFF | 0.3 | Auto |

| | |
|---|---|
| Tune Mode #2: | He |
| Quick Scan | ON |
| Independent P/A Factors | ON |
| Stabilization Time | 30 sec |

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## Acquisition Method

| | | | | |
|---|---|---|---|---|
| Scan Type | Single Quad | | | |
| Number of Masses | 19 | | | |
| Element Name | Mass | +0.5 u | IntegTime/ Mass [sec] | Detector Mode |
| Al | 27 | OFF | 0.9 | Auto |
| Sc | 45 | OFF | 0.3 | Auto |
| V | 51 | OFF | 1.5 | Auto |
| Cr | 52 | OFF | 3 | Auto |
| Fe | 56 | OFF | 0.3 | Auto |
| Co | 59 | OFF | 0.3 | Auto |
| Ni | 60 | OFF | 3 | Auto |
| Cu | 63 | OFF | 0.3 | Auto |
| As | 75 | OFF | 3 | Auto |
| Se | 78 | OFF | 15 | Auto |
| Y | 89 | OFF | 0.3 | Auto |
| Mo | 95 | OFF | 0.3 | Auto |
| Ru | 101 | OFF | 0.3 | Auto |
| Rh | 103 | OFF | 0.3 | Auto |
| Pd | 105 | OFF | 3 | Auto |
| In | 115 | OFF | 0.3 | Auto |
| Tb | 159 | OFF | 0.3 | Auto |
| Pt | 195 | OFF | 3 | Auto |
| Bi | 209 | OFF | 0.3 | Auto |
| Tune Mode #3: | O2 | | | |
| Quick Scan | OFF | | | |
| Independent P/A Factors | ON | | | |
| Stabilization Time | 30 sec | | | |
| Scan Type | MS/MS | | | |
| Number of Masses | 5 | | | |
| Element Name | Q1 -> Q2 | +0.5 u | IntegTime/ Mass [sec] | Detector Mode |
| Sc | 45 -> 61 | OFF | 0.3 | Auto |
| V | 51 -> 67 | OFF | 1.5 | Auto |
| As | 75 -> 91 | OFF | 3 | Auto |
| Se | 78 -> 94 | OFF | 15 | Auto |
| Y | 89 -> 105 | OFF | 0.3 | Auto |

[MONITOR]
Monitor Mass
Mass
(Numerator) (Denominator)
111
201
202

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## Acquisition Method

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| | | |
|---|---|---|
| [PERIPUMP/ISIS] | | |
| Sample Introduction | General | |
| | | |
| PeriPump/ISIS Settings | | |
| Pre Run | | |
| Uptake Speed (Nebulizer Pump) | 0.3 | rps |
| Uptake Time | 60 | sec |
| Stabilize | 60 | sec |
| | | |
| Post Run (Probe Rinse) | | |
| Rinse Speed (Nebulizer Pump) | 0.2 | rps |
| Rinse at Rinse Port (Sample) | 30 | sec |
| Rinse at Rinse Port (Std) | 30 | sec |
| | | |
| Post Run (Rinse) | | |
| Rinse Vial 1 | 1 | |
| Rinse Speed (Nebulizer Pump) | 0.3 | rps |
| Rinse at Rinse Vial (Step 1) | 150 | sec |
| Rinse at Rinse Port (Step 1) | | sec |
| Rinse Vial 2 | | |
| Rinse Speed (Nebulizer Pump) | | rps |
| Rinse at Rinse Vial (Step 2) | | sec |
| Rinse at Rinse Port (Step 2) | | sec |
| Rinse Vial 3 | | |
| Rinse Speed (Nebulizer Pump) | | rps |
| Rinse at Rinse Vial (Step 3) | | sec |
| Rinse at Rinse Port (Step 3) | | sec |
| | | |
| Intelligent Rinse | | |
| Intelligent Rinse | Off | |
| | | |
| Preemptive Rinse | | |
| Preemptive Rinse | Off | |
| | | |
| [TUNE] | | |
| Tune Way | Auto Tune | |
| | | |
| Tune Mode #1: | No Gas | |
| (Scan Type) | | |
| Scan Type | Single Quad | |
| | | |
| (Plasma) | | |
| Plasma Mode | Low Matrix | |

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## Acquisition Method

| | | |
|---|---|---|
| (Lenses) | | |
| Extract 2 | -150 | V |
| Omega Bias | -80 | V |
| Omega Lens | 7.4 | V |
| Q1 Entrance | -6 | V |
| Q1 Exit | -2 | V |
| Cell Focus | -1 | V |
| Deflect | 11.4 | V |
| | | |
| (Q1) | | |
| Q1 Bias | -4 | V |
| Q1 Prefilter Bias | -36 | V |
| Q1 Postfilter Bias | -10 | V |
| | | |
| (Cell) | | |
| Use Gas | No | |
| He Flow | Off | |
| He Flow Rate | 0 | mL/min |
| H2 Flow | Off | |
| H2 Flow Rate | 0 | mL/min |
| 3rd Gas Flow | Off | |
| 3rd Gas Flow Rate | 0 | % |
| 4th Gas Flow | Off | |
| 4th Gas Flow Rate | 0 | % |
| OctP RF | 120 | V |
| Energy Discrimination | 5 | mV |
| | | |
| Tune Mode #2: | He | |
| (Scan Type) | | |
| Scan Type | Single Quad | |
| | | |
| (Plasma) | | |
| Plasma Mode | Low Matrix | |
| | | |
| (Lenses) | | |
| Extract 2 | -150 | V |
| Omega Bias | -80 | V |
| Omega Lens | 7.4 | V |
| Q1 Entrance | -6 | V |
| Q1 Exit | -2 | V |
| Cell Focus | -1 | V |
| Deflect | -5.2 | V |
| | | |
| (Q1) | | |
| Q1 Bias | -4 | V |
| Q1 Prefilter Bias | -36 | V |

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## Acquisition Method

| | | |
|---|---|---|
| Q1 Postfilter Bias | -10 | V |
| | | |
| (Cell) | | |
| Use Gas | No | |
| He Flow | Off | |
| He Flow Rate | 5 | mL/min |
| H2 Flow | Off | |
| H2 Flow Rate | 0 | mL/min |
| 3rd Gas Flow | Off | |
| 3rd Gas Flow Rate | 0 | % |
| 4th Gas Flow | Off | |
| 4th Gas Flow Rate | 0 | % |
| OctP RF | 200 | V |
| Energy Discrimination | 5 | mV |
| | | |
| Tune Mode #3: | O2 | |
| (Scan Type) | | |
| Scan Type | MS/MS | |
| | | |
| (Plasma) | | |
| Plasma Mode | Low Matrix | |
| | | |
| (Lenses) | | |
| Extract 2 | -150 | V |
| Omega Bias | -80 | V |
| Omega Lens | 7.4 | V |
| Q1 Entrance | -6 | V |
| Q1 Exit | -2 | V |
| Cell Focus | -1 | V |
| Deflect | 5 | V |
| | | |
| (Q1) | | |
| Q1 Bias | 2 | V |
| Q1 Prefilter Bias | -14 | V |
| Q1 Postfilter Bias | -6 | V |
| | | |
| (Cell) | | |
| Use Gas | No | |
| He Flow | Off | |
| He Flow Rate | 0 | mL/min |
| H2 Flow | Off | |
| H2 Flow Rate | 0 | mL/min |
| 3rd Gas Flow | Off | |
| 3rd Gas Flow Rate | 0 | % |
| 4th Gas Flow | Off | |
| 4th Gas Flow Rate | 30 | % |
| OctP RF | 200 | V |

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## Acquisition Method

| | | |
|---|---|---|
| Energy Discrimination | -7 | mV |

## Appendix F—Sampling and analytical procedure for the analysis of contaminant elements in gases for medicinal applications by University of Florence (Italy)

**Unpublished paper**

Franco Tassi

*Department of Earth Sciences, University of Florence, Florence, Italy*

Samples for the analysis of contaminant elements in gases medical applications are collected using a chemical trap (CT) consisting of two glass bubblers, having an inner volume of 150 cc. The bubblers which are preventively cleaned in a suprapur HCL bath and abundantly rinsed with MilliQ, are filled with 50mLof 1% $HNO_3$ acidified MilliQ water and connected in series to the gas outlet equipped with a flux regulator. The gas is flushed through the CT at a controlled flux (300cc/min) and ambient temperature. The amount of gas flushed (about 0,5 mc) depends on the sensitivity requested, considering that the target detection limits of the analytes are to be consistent with those regulated by law for medical applications. Once the sampling phase is completed the acidified solution is stored into polyethylene bottles to be analysed by inductively coupled plasma spectrometry (ICP-MS 7500CE) for the determination of Cd, Pb, As, Hf, Co, V, Ti, Au, Pd, Os, Rh, Se, AG, Pt, Li, Sb, Ba, Mo, Cu, Sn and Cr without further treatments according to the procedures described by the US Environmental Protection Agency (EPA6020A).

The CT (chemical solution, geometry of the glass line) and the operational parameters (e.g. gas flux) were selected after specific tests, carried out to verify the efficiency of the trapping method. These tests showed that the CT allowed to obtain a high reproducibility, demonstrating that (i) the contaminant elements were completely dissolved in the acidic solution, i.e. no analytes were lost during the sampling procedure, and (ii), *memory effect* was absent.

The ICP-MS analyses are accredited by ACCREDIA, the latter being the Italian National Accreditation Body appointed by the state to perform accreditation activity, i.e. certifying the quality of the analytical data obtained. Internal standards to set up the ICP-MS are $^{6}Li$, $^{45}Sc$, $^{89}Y$ and $^{115}In$. Standard solutions were prepared by opportune dilution of each single element starting from 1000 mg/L solutions. The ICP-MS techniques has (i) a low detection limit (down to 0.01 µg/L), (ii) a relatively low analytical error (5%) and (iii) the capability to determine a high number of elements in the same analytical run. The selected analytical method minimizes the risk for sample contamination during the sampling and analytical operations, which represents a fundamental advantage warranting relatively high accuracy and precision.

**References**

Capecchiacci, T., Tassi, F., Vaselli, O., 2017 Contamination Test of Metal and Non-Metal Elements from Copper Gas Pipe to Food Gases. Packaging Technology and Sciences, in press.
Capecchiacci, T., Tassi, F., Vaselli, O., 2014. Migration Processes of Metal Elements from Carbon Steel Cylinders to Food Gases. Packaging Technology and Sciences, 26, 787-797, doi: 10.1002/pts 2069.
Capecchiacci, T., Tassi, F., Vaselli, O., 2014., Test di Migrazione in $CO_2$ per uso alimentare di contaminanti metallici da serbatoi in acciaio. CNR-IGG Internal Report n.11119.pp. 1-2

## Appendix G—Questions and answers

Q: Why is there a different pressure for the sampled cylinders and therefore the sample of the cylinders is not homogenous?

A: In the different markets in the EU and Asia, there are different marketing authorisations existing or local regulation/legislation which have indicated different pressures for the cylinders. For example, in the UK the marketing authorisation for the oxygen cylinders indicates a pressure of 230 bar instead of 200 bar for most of the other countries in Europe. For the cylinder samples taken, only products were used that are filled under a marketing authorisation. Furthermore, the regulator in the VIPR reduces the cylinder pressure to the nominal outlet pressure (4 bar) defined in ISO 10524-3, *Pressure regulators for use with medical gases -- Part 3: Pressure regulators integrated with cylinder valves* [5].

There is no documented evidence that the filling pressure has any influence on the particle generation within the CCS. That is why the pressure does not impact on the homogeneity of the sample.

Q: Why is the QL of the test done for vanadium so close or identical to the 30% limit of the PDE?

A: The tests were initially designed to demonstrate that the results are below the PDE and not the 30% limit of the PDE. It was decided not to repeat the tests with the lower QL as the results showed that the EI were below the ICH Q3D limits, especially taken into account that the measured results for the Vanadium were close or even below the DL.

Q: Why are there some negative results?

A: This is because the blank solution could not be prepared totally free of the elements concerned. Therefore, if the tested sample has lower values as the blank solution, these results will be indicated as negative results in this report.

Q: Has the method been validated?

A: Yes, the ICP-MS is a validated method, nevertheless the sampling method is a non-validated method but based on best practices.