



Compressed Gas Association

The Standard For Safety Since 1913

CGA M-25—2020

ICH Q3D RISK ASSESSMENT REPORT ELEMENTAL IMPURITIES IN MEDICINAL GASES

FIRST EDITION

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PREFACE

As part of a program of harmonization of industry standards, the Compressed Gas Association (CGA) has issued CGA M-25, *ICH Q3D Risk Assessment Report Elemental Impurities In Medicinal Gases*, jointly produced by members of the International Harmonization Council and originally published by the 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 harmonized standard for the worldwide use and application of all members of 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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Work Item 19-141
Medical Gases Committee

FIRST EDITION: 2020

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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 EIGA 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.

2 Scope and purpose

2.1 Scope

The scope of this publication covers all packaged medicinal gases as listed below produced by EIGA members and approved as designated medical gases by the U.S. Food and Drug Administration (FDA) or authorised as medicinal products in other 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 as follows:

- oxygen;
- synthetic medical air;
- medical air;

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

- carbon dioxide;
- nitrous oxide;
- nitrogen;
- xenon;
- helium;
- 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); and
- 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.

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 Medicinal gases

Includes the designated medical gases in the United States as well as other gases approved through a market authorization.

3.2.4 Permitted daily exposure (PDE)

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

4 EIGA'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, in 22,5L.	Acute treatment 22,5L
Nitrous oxide	Nitrous oxide for anesthetics is used with a concentration of N ₂ O 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
N ₂ O/O ₂ mixtures	See nitrous oxide and oxygen, but as the mixture is not 70% N ₂ O but only 50%, for short term treatment using the analgesic effects, the results are 2250L for N ₂ O and 2250L for oxygen. So 4500L in total for the mixture.	Acute treatment 4500L
NO/N ₂ mixtures	40 ppm of NO is the maximum dose given to the patient, Considering the minimal dose of NO 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. 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)
He/O ₂ mixtures	See helium with 8640L of He and 2160L of oxygen. 10800L in total for the mixture.	Acute treatment 10800L
CO ₂ /O ₂ mixtures	See carbon dioxide with 22,5L of CO ₂ 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

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 steel valves and steel cylinders)	Investigation through 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 $\mu\text{g/day}$;
- 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 be achieved 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 1×10^{-7} µg/mL to 1×10^{-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.

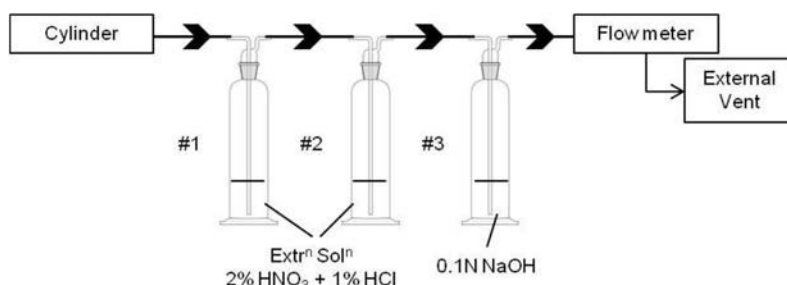


Figure 2—Testing setup with the three Drechsel bottles

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.

EIGA 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 inconsistencies, 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