TECHNICAL BULLETIN

Prepared by WG-7 TB 33/19 – October 2019

Elemental Impurity Product Risk Assessment Summary

Introduction

This Technical Bulletin is intended to be used to prepare the overall elemental impurity product risk assessment summary for Module 3.2.P.5.5 (Characterisation of Impurities) and needs to be adapted for the specific product under consideration.
The text between <> shall be exchanged for the specific product.
This TB is a template and is below used for <nitrous oxide> as an example.

Elemental impurity product risk assessment summary for <nitrous oxide>

<Nitrous oxide> is composed of the active ingredient <nitrous oxide> in accordance with the Ph. Eur., current version. <There are no further excipients>. Potential impurities resulting from the specification of the drug substance < (and excipients)> are discussed in module 3.2.P.5.6 (Justification of Specification(s)).
For the assessment of EIs in the finished product we refer to an assessment performed by EIGA members to determine whether medicinal gases like <nitrous oxide> are likely to contain any elemental impurities (EIs), specified in ICH Q3D. For this purpose, the potential sources for EIs listed below were considered:

- active pharmaceutical ingredients,
- excipients,
- medicinal gas manufacturing and filling processes,
- potential contributions of manufacturing equipment,
- container closure system (CCS), including their maintenance.

Although the method of production of the active substance is unique for each medicinal gas, the method of filling and packaging the gases is common across all products and manufacturers. The same basic equipment and procedures are used to fill these products and the container closure systems (CCS) including pressure and flow regulation for patients' application, used are similar for all products. This led to the conclusion that the contribution to the potential presence of EIs given by the filling and packaging was the same for all medicinal gases.

Looking at the Maximum Daily Dose (MDD) of various medicinal gases, was evident that oxygen is that with the highest MDD.
MDD data for oxygen and <nitrous oxide> are detailed in the <table below>*:

Product	Calculation / Explanation	Maximum Daily Dose
Oxygen	The MDD applies to acute treatment.	Acute treatment 10800L
Nitrous oxide	Nitrous oxide for anaesthetics is used with a	Acute treatment

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	concentration of N2O up to 70% in oxygen. The maximum duration of treatment is 10h, resulting in 3150L.	3150L
N2O/O2 mixtures	See Nitrous oxide and oxygen, but as the mixture is not 70% N2O but only 50%, for short term treatment using the analgesic effects, the results are 2250L for N2O and 2250L for oxygen. So 4500L in total for the mixture.	Acute treatment 4500L

* the table must be adjusted to the product in consideration, always keeping the oxygen as the reference product

The MDD of <Nitrous oxide> is <one third> of that of oxygen.
This allows to consider the outcome of the assessment carried out on oxygen as representative for all medicinal gases when following a worst-case approach.
Thus, even if there is no “leaching” from the metal equipment and container closure system to a gas, because of the remote possibility of particles entrainment, a test on some representative samples has been carried out.

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 and, thus, has the highest Maximum Daily Dose;
- 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 (Valve with Integrated Pressure Regulator) used as the closure for the primary packaging of the CCS is the most likely source of particulate in the product, thus represents the worst-case scenario;
- 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(g), 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, (MA).

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)
- Group 3 elements: molybdenum (Mo), copper (Cu), tin (Sn) and chromium (Cr)

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, to determine whether the EIs would be within the permitted daily exposure (PDE) limits detailed in ICH Q3D.
From the information given in the EIGA report attached to this module, the levels of EIs within the medicinal gases which are used for patient treatment are below the limits set out in ICH Q3D.
For further details please refer to the attached EIGA Report ICH Q3D RISK ASSESSMENT REPORT ELEMENTAL IMPURITIES IN MEDICINAL GASES, Doc 216/19.

Following table shows the presence of EI in the different steps in the manufacturing process as a summary of elemental impurity data for potential components.

Element	ICH Q3D class	API Synthesis & starting material	Intentionally added	In Excipients	Coming from manufacturing equipment	Leached from CCS	Action	Max. Measured results µg/day	Control Threshold (30% of PDE)
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 of the worst-case product	0.672	1.5
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 of the worst-case product	0.083	0.3
Nickel (Ni)	2A	No	No	No	Yes (stainless steel and steel)	Yes (stainless steel valves and steel cylinders)	Investigation through commercially available batches of the worst-case product	0.678	1.5
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		

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Element	ICH Q3D class	API Synthesis & starting material	Intentionally added	In Excipients	Coming from manufacturing equipment	Leached from CCS	Action	Max. Measured results µg/day	Control Threshold (30% of PDE)
Molybdenum (Mo)	3	No	No	No	Yes (stainless steel and steel)	Yes (stainless steel valves and steel cylinders)	Investigation through commercially available batches of the worst-case product	0.062	3
Copper (Cu)	3	No	No	No	Yes	Yes (brass valves and aluminium alloy cylinders)	Investigation through commercially available batches of the worst-case product	0.491	9
Tin (Sn)	3	No	No	No	Yes (brass)	Yes (brass valves)	Investigation through commercially available batches of the worst-case product	0.101	18
Chromium (Cr)	3	No	No	No	Yes (stainless steel)	Yes (stainless steel valves and aluminium alloy cylinders)	Investigation through commercially available batches of the worst-case product	0.392	0.9

Table: Presence of EI in the different steps in the manufacturing process
Summary of elemental impurity data for potential components

Conclusion

Oxygen, being the gas with the highest Maximum Daily Dose, has the lowest control threshold.
Considering the Maximum Daily Dose, <nitrous oxide> would have a control threshold <three> times greater.
The contribution of the filling process to EIs in the finished product is assumed to be the same for all the gases.
Thus, the same content of EIs is expected to be found in <nitrous oxide>.
The tested samples of oxygen show an actual concentration of EIs well below the control threshold. Thus, no further testing for <nitrous oxide> is required.
The above allows the conclusion that for <nitrous oxide> the presence of EIs is below the control threshold and no further testing is required.

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