CGA

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

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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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.