TECHNICAL BULLETIN

Prepared by WG-7 TB 054/24 – May 2024

Shortage Prevention Plan

Helium / Helium Mixtures

Introduction:

This document covers the medicinal product helium (He) with an assay of more than 99,5% (V/V) and Helium mixtures with concentrations up to 79% of helium in oxygen (O2). The active substance in these mixtures is helium.

Helium, according to European Pharmacopoeia (monograph 2155) is produced by separation from natural gas.

The pure helium is compressed in steel or aluminum cylinders. The helium mixtures involve a further process of mixing with oxygen in steel or aluminum cylinders.

In all cases the product can be administered to patients only in combination with oxygen at a minimum concentration of 21% (v/v) in the breathing gas.

Usually, helium/helium mixtures are supplied to healthcare facilities as licensed drugs in defined packages as gaseous mixture compressed in aluminum or steel cylinders.

EIGA emphasizes that in Europe at no time was there a shortage of helium / helium mixtures to patients in healthcare facilities.

EIGA has used Technical Report No. 68, “Risk-Based Approach for Prevention and Management of Drug Shortages”, as prepared by the Parenteral Drug Association (PDA) in 2014 as part of the inter-association collaborative contribution to the EMA (European Medicines Agency) Initiative on medicinal product shortages caused by manufacturing and GMP compliance issues. The document can be freely downloaded from the PDA website.
The risk triage method is a simple four-step process that uses a preliminary hazards analysis approach to evaluate the risk of a drug shortage by considering the therapeutic use of a product, availability of alternatives, and likelihood of occurrence. The process assigns a risk priority level based on a combination of the potential impact to the patient and likelihood of a drug shortage, and then recommends risk controls for the assessed product. The method uses discrete information and key words to assign a priority level for each element, making the assessment focus on product information and avoiding discussions on general subjective terms.

The steps in the triage process are as follows:

1. Identify risk level (impact to patient) based on therapeutic use and availability of alternatives.
2. Determine the likelihood of a drug shortage for the product.

***EUROPEAN INDUSTRIAL GASES ASSOCIATION** AISBL*
AVENUE DE L’ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 ♦ E-mail : info@eiga.eu - www.eiga.eu

3. Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product.

4. Plan and implement the suggested risk controls for the assessed product based on the risk priority level.

Step 1:

			Availability of Alternatives		
			No Alternatives Available	Alternative Products Available: Similar Therapy	Exact Product Available but in Other Presentations
Therapeutic Use & Consequences if Product is not Available	Medically necessary product, life supporting or life sustaining	Fatal or severe irreversible harm if the patient is not treated with the product	**Risk Level A**	**Risk Level A**	**Risk Level B**
	Acute short term or chronic long term	Severe harm but reversible if patient is not treated with the product	**Risk Level A**	**Risk Level B**	**Risk Level C**
	Other indications	inconvenience if patient is not treated with the product	**Risk Level B**	**Risk Level C**	**Risk Level C**

Typical Indications of helium/helium mixtures are:
Because of its low density helium flows through an orifice much more easily than other medical gases.
Helium is used with a least 21% oxygen in the following circumstances:

- To assist the flow of oxygen into the alveoli of patients with severe respiratory obstruction.
- To prevent atelectasis
- In various concentrations, in conjunctions with air or oxygen, for gas transfer lung function tests (for lung function mixtures please refer to the respective document).

Therefore, the assessment is that helium/helium mixtures are for acute short term or chronic long term uses. Furthermore, it should be noted that for inhaled helium/helium mixtures there are other alternatives addressed to the underlying causes (e.g. mucolytic agents, antibiotics).
In the assessment of alternatives, the outcome is that there are many “Exact products available” as there are other Marketing Authorisation Holders (MAHs) in the countries were having authorisation for helium/helium mixtures. It should also be noted that these products are present in the exact same presentation, therefore lowering the risk even further.
With the assessment of “Therapeutic Use & Consequences if Product is not Available” as “Acute short term or chronic long term uses” and “Availability of Alternatives” as “Exact Product Available” – it is classed as **RISK LEVEL C.**

Step 2:

For the likelihood analysis, the following main sources of hazards were assessed:

according to the following criteria:

LOW: Robust controls exist for a hazard

MODERATE: Limited controls exist for a hazard

HIGH: No controls exist for a hazard

Drug Substance:

Natural gas reservoirs are the conventional source of commercial helium gas. They contain various amounts of helium, ranging from negligible to 7%. The economically exploited helium reserves are located in the USA, Qatar, Algeria and Russia.

Even though helium plays an important role in the medical field (e.g. as a coolant for superconducting magnets in medical diagnostic equipment such as MRI, which accounts for around 30% of all helium usage), it is not primarily intended for use as an active pharmaceutical ingredient (API) for human medicinal products. Only a very small amount of the produced helium is used as an API.

Manufacturing (quality control of the industrial product under GMP conditions to be qualified as an API) is performed directly within the EU with short delivery times and stable production in accordance with GMP requirements. Transportation of the drug substance is performed either directly on the site where the finished product is manufactured, or in cylinders loaded onto trucks and transported by road. Drug substance manufacturers are normally located within a few hours from the finished product manufacturing site.

- ✓ Back up available
- ✓ Production already located within European Union
- ✓ Short transport routes if not onsite
- ✓ Well established and highly reliable process producing high quality products
- ✓ Sufficient minimum stocks of drug substance at the manufacturing site stable for a very long time.

→ Few manufacturing sites

➔ ***The resulting risk of failure of Drug Substance supply is considered:***

MODERATE

Step 2 - continued:

Drug Product & Packaging:

The drug product consists only of the drug substance or of the drug substances helium and oxygen (with the oxygen also being produced usually via air separation, therefore making it readily available), filled into aluminum/steel cylinders of different sizes, mounted with different valves and transported via road trucks directly to hospitals. The packaging, i.e. cylinder and valve combination, used for medicinal gases are unique, in that they are reused when the cylinders are returned to the finished product manufacturer for refilling. Generally, the cylinders and valves are in use for at least 10 years, sometimes much longer. The supply of these packaging materials can be considered highly reliable as there are several manufacturers within the EU for cylinders, vessels and valves.

Electricity supply for the manufacturing of the drug substance as well as for the drug product filling equipment has historically been reliable and is, therefore, not considered to be a significant contributory factor to the risk of product shortage. The finished product is stored at ambient temperature rendering stocks independent from electricity supply as the product is stored as a compressed gas in cylinders.
The drug product is generally manufacture by compressing the drug substance into cylinders or by mixing the helium with oxygen and compressed and filled into cylinders, making the manufacturing process extremely stable and consistent.

The equipment for manufacturing is relatively simple, consisting of mainly reservoirs, piping, valves and filling hoses, with the aging of equipment therefore not considered a potential reason for product shortages. Quality defects are rare (< 1%) due to batch sizes generally being relatively small, resulting in closely managed quality control processes. This also means that any reject decision only affects a relatively small quantity of cylinders.
The cylinders are labeled with an outer label, batch label and, in some regions, a patient information leaflet. Stocks of pre-printed packaging material are usually kept at the manufacturing site and can be readily obtained from local suppliers; batch labels are printed in-house.
The cylinder/vessel is the final packaging and no relabeling is done.

- ✓ Simple production process
- ✓ Drug product consist of only the drug substance, drug substance stock usually quite large
- ✓ Simple drug substance
- ✓ Reusable packages (min. 10 years) and reliable packaging manufacturers
- ✓ Aging of equipment negligible
- ✓ High quality products, < 1% OOS, additional small batch sizes with short lead times and large number of quality controls

➔ ***The resulting risk of failure of Drug Product manufacturing and packaging is:***

LOW

Step 2 - continued:

Warehouse Distribution & Affiliates:

In the vast majority of cases the Marketing Authorisation Holder (MAH) is also the manufacturer, with transportation of the finished product often being directly managed to the end user/customer.There can be minimum stocks for certain sizes, however, to trace them in national databases or the EMA is not necessary as package sizes are exchangeable, as generally they are intended to be multi-dose, multi-patient packages.

➔ ***The resulting risk of failure of Warehouse Distribution & Affiliates is:***

LOW

Wholesaler & Pharmacy:

Wholesaler and Pharmacies are not commonly used in the supply chain of Helium/Helium mixtures as the distribution is mainly performed directly by the Marketing Authorization Holders/Manufacturer.

➔ ***The resulting risk of failure of Wholesaler & Pharmacy is:***

LOW

Conclusion for the Likelihood of Shortage:
Considering that, all parts of the supply chain: “Pharmaceutical product and packaging”, “Warehouse distribution and subsidiaries” and “Wholesaler and pharmacy” are considered low risk, with the exception of Drug substance being classified as moderate; we could consider the resulting overall risk as:

MODERATE

Step 3 - Determine the risk priority level based on a combination of impact to patient and likelihood of a drug shortage for the product:

Therapeutic Use & Consequneces if Product is not Available		Likelihood of Shortage		
		High	Moderate	Low
	Risk Level A	Risk Priority Level 1	Risk Priority Level 1	Risk Priority Level 2
	Risk Level B	Risk Priority Level 1	Risk Priority Level 2	Risk Priority Level 3
	Risk Level C	Risk Priority Level 2	Risk Priority Level 3	Risk Priority Level 3

With the assessment of "Therapeutic Use & Consequences if Product is not Available" as "**RISK LEVEL C** and the assessment "Likelihood of Shortage" as **MODERATE** the outcome is **RISK PRIORITY LEVEL 3**.

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 ♦ E-mail : info@eiga.eu - www.eiga.eu

Step 4 - Plan and implement the suggested risk controls based on the risk priority level:
Depending on the risk level the following controls are suggested by the PDA document, see table:

Risk Priority	Suggested Controls
Level-1	• Appropriate inventory and safety stock management • Multisite sourcing with higher manufacturing capacity reserves • Supplier management controls (see **sec. 5.4** of TR54) • Supply chain/transportation line security, business continuity and communication plan • Extended Value Stream Mapping (VSM)
Level-2	• Consider multisite sourcing • Value Stream Mapping (VSM) • Proactive inventory management • Process capability and robustness exercised (with Quality Metrics)
Level-3	• Generally accepted risk level

Conclusion:
EIGA assessed the medicinal Helium/Helium mixtures supply chain and all associated risks and concluded that for medicinal Helium/Helium mixtures the **RISK PRIORITY LEVEL 3** is appropriate with the residual risk of a drug shortage being generally accepted.
Therefore, it is proposed that there is no necessity to prepare additional SHORTAGE MITIGATION PLAN (SMP) as the risk of drug shortage can be generally accepted.
EIGA also recommends that Helium/Helium mixtures should be assessed as **not** required to be included in the "Union list of critical medicines" as the security in the supply and prevention of shortages is assured.
EIGA recommends that this SHORTAGE PREVENTION PLAN (SPP) can be used for all EIGA member companies.

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 ♦ E-mail : info@eiga.eu - www.eiga.eu