TECHNICAL BULLETIN

Prepared by WG-7 TB 055/24 – May 2024

Shortage Prevention Plan

Lung Function Gas Mixtures

Introduction:

This document covers the medicinal products for Lung Function testing, these can include the following drug substances Carbon Monoxide (CO) as 5% (V/V) Intermix in Nitrogen according to European Pharmacopoeia (monograph 2904), Methane (CH_4) as 2% (V/V) Intermix in Nitrogen according to European Pharmacopoeia (monograph 2905), Acetylene (C_2H_2) as 1% (V/V) Intermix in Nitrogen according to European Pharmacopoeia (monograph 2903), Helium (He) according to European Pharmacopoeia (monograph 2155) and Oxygen (O_2) according to European Pharmacopoeia (monograph 0417) and Nitrogen (N_2) according to European Pharmacopoeia (monograph 1247 or 1685) as excipients.

Typical mixtures contain a very low percentage (less than 0,5% (V/V)) of CO to determine the lungs` diffusion capacity and low percentages (less than 0,5% (V/V)) of CH_4 and/or C_2H_2 or Helium (in concentrations up to 20% (V/V)) to determine the lung volume and pulmonary blood flow. Additionally, to breath the mixture safely there must be approximately 21% (V/V) Oxygen (in those mixtures considered excipient). The rest of these mixtures consists of the excipient Nitrogen.

For the mentioned drug products the manufacturing plants are primarily used to produce industrial grade products in a non GMP environment and these products are only used to a minor (negligible) extend for medicinal purposes, therefore the drug substances are only to be considered as suitable for manufacturing a medicinal product after it has been tested, certified, and assigned for medicinal use in a GMP environment (e.g. in the finished product manufacturing site).

After testing, certifying, and assigning the drug substances for medicinal use they are mixed by weight into their respective portions into aluminium cylinders.

Usually, lung function test gas mixtures are supplied to healthcare facilities as licensed drugs in defined packages as gaseous mixture compressed in aluminum cylinders.

EIGA emphasizes that in Europe at no time was there a shortage of lung function gas 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

***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

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.
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 Lung function test gas mixtures are:

- for diagnostic testing of lung function with determination of the lungs` diffusion capacity (or transfer factor) as the main parameter, and of lung volumes and pulmonary blood flow, as additional parameter.

Therefore, the assessment is that Lung function test gases are ‘other indications’.
In the assessment of alternatives, the outcome is that there are many “Exact products available” as there are many Marketing Authorisation Holders (MAHs) within each EU member state having authorisations for Lung function test gases. 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 “Other indications” 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:
The drug substances used for the drug products can be divided into two conventional groups:

One formed by flammable gases, i.e. acetylene, carbon monoxide and methane,

and one formed by inert gases, namely helium.

For the first group, since there is a risk of ignition when a flammable gas is mixed with oxygen, even at relatively low concentration levels, it is necessary to mix the flammable gas with nitrogen to ensure that it is below the level of flammability at which it self-ignites. In order to safely produce gas mixtures for lung function tests, three intermixes have been produced in which nitrogen is used to reduce the flammability of acetylene (2903), carbon monoxide (2904) and methane (2905). If an intermix is used as a safe means of adding the drug substance to the final product, the intermix should be considered as the API and only its production controlled under GMP-compliant conditions (avoiding the need to use a GMP-compliant QMS to control the manufacture of the flammable gas).

As far as helium (group of inert gases) is concerned, the production facilities are mainly used to produce industrial-grade products in a non-GMP-compliant environment, while the helium used for medicinal purposes is in very small quantities; therefore, helium is only qualified as a medicinal substance after it has been tested, certified and assigned for medicinal use in a GMP-compliant environment (e.g. at the manufacturing site of the finished product).

Therefore and because of the very low concentrations of these gases in the lung function test gas mixtures used the risk of shortages of these gases can be considered very low.

There are several manufacturing plants for the mentioned drug substances within the European Union that can produce more drug substances than are required for patient use across Europe.
Manufacturing 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
- ✓ low possibility of shortage of starting materials (commodity products)
- ✓ 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.

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

LOW

EUROPEAN INDUSTRIAL GASES ASSOCIATION *AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
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Step 2 - continued:

Drug Product & Packaging:

The drug product consists of the several drug substances and the excipients Oxygen and Nitrogen. (with the oxygen and nitrogen being produced via air separation, therefore making it readily available), filled into aluminum 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 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 manufactured by using the necessary amounts of the intermixes where nitrogen is used to reduce the flammability of C_2H_2, CH_4 and CO and the necessary amounts of He, O_2 and N_2. This is normally done by weighing in the components one after the other. The result after homogenisation of the mixture is the final drug product with a certain pressure in the container closure system – e.g. the cylinder mounted with a valve, 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 is the final packaging and no relabeling is done.

- ✓ Simple production process
- ✓ Drug product consist of the mentioned the drug substances, drug substance stocks are usually quite large
- ✓ Simple drug substance – readily available
- ✓ 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 lung function test gas 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:
As all parts of the supply chain “Drug Substance”, “Drug Product & Packaging”, “Warehouse Distribution & Affiliates” and “Wholesaler & Pharmacy” are considered to be low risk, the overall resulting risk is considered:

LOW

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 **LOW** the outcome is **RISK PRIORITY LEVEL 3**.

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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 lung function test gas mixtures supply chain and all associated risks and concluded that for lung function test gas 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 lung function test gas 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.

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