TECHNICAL BULLETIN

Prepared by WG-7 TB 058/24 – May 2024

Shortage Prevention Plan

Medicinal Oxygen

Introduction:

This document covers the medicinal product Oxygen, with an assay of more than 99,5% (V/V) and produced via the cryogenic distillation of ambient air. The product has a Ph.Eur. monograph, 0417, for many years and is one of the most commonly used medicinal products worldwide. Usually, medicinal oxygen is supplied to healthcare facilities as a licensed medicinal product in defined packages, most commonly in large volumes as a liquid product stored at the healthcare facility site in insulated storage tanks and distributed via the medical gas pipeline supply system owned and operated by the healthcare facility. Smaller healthcare facilities, care homes and individual patients at home are generally supplied with gaseous oxygen compressed in cylinders or as a liquid in small cryogenic vessels.

EIGA emphasizes that in Europe, and as confirmed to the European Medicines Agency (EMA), during the COVID-19 pandemic our members confirmed that at no time was there a shortage of oxygen to patients in healthcare facilities or for home oxygen use. Due to the significant increase in demand for oxygen during the COVID-19 pandemic, some issues were encountered in relation to equipment and manpower, but these were resolved via regulatory flexibilities agreed to by national authorities.

Lessons have been learned from the COVID-19 pandemic, with respect to the design and operation of gas supply systems and pipeline distribution systems, and as such the industry has renewed its commitment to review and improve relevant standards associated to medical oxygen production and distribution methods, via increased active participation in regional and national standardization bodies, such as ISO and ANSI, in order to ensure that the lessons learnt from the COVID-19 pandemic are incorporated into the relevant standards.

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.

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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 medicinal Oxygen:
Normobaric oxygen therapy (Oxygen therapy at normal pressure):

- Treatment or prevention of hypoxia and hypoxaemic conditions.
- Treatment of cluster headache.

Hyperbaric oxygen therapy (Oxygen therapy at high pressure)

- Treatment of serious carbon monoxide poisoning irrespective of the COHb content in the blood (in particular essential in patients who after exposition to carbon monoxide have lost consciousness, have neurological symptoms, cardiovascular failure or serious acidosis or pregnant patients).
- Treatment of decompression sickness, or of air/gas embolism of a different origin.
- As supporting treatment in cases of osteoradionecrosis.
- As supporting treatment in cases of clostridial myonecrosis (gas gangrene).

Therefore, the assessment is that Oxygen is a medically necessary product and is life supporting and life sustaining.
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 medicinal oxygen. 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 “Medically necessary product, life supporting or life sustaining” and “Availability of Alternatives” as “Exact Product Available” – it is classed as **RISK LEVEL B.**

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:
For oxygen, the drug substance is considered to be oxygen manufactured at Air Separation Units (ASUs) via the cryogenic distillation of ambient air. There are many ASUs within each member state that can produce significantly more oxygen than is required for patient use across Europe, with only a small percentage of oxygen produced at an ASU being used for healthcare purposes. Manufacturing of oxygen is performed directly in the EU, with associated short delivery times and via a very stable production process in accordance with GMP requirements. Manufacture of the drug substance is performed either directly on the site of the manufacture of the finished product or is transported to the finished product manufacturing site via road tanker by road. The location of the drug substance manufacturer, when different to the finished product manufacturing site, is usually within a few hours from the finished product manufacturing site.

- ✓ Back up available
- ✓ Production already located within European Union
- ✓ No possibility of shortage of starting material (ambient air)
- ✓ Short transport routes if not onsite
- ✓ Well established and highly reliable process producing high quality products, no deliveries with OOS over the last period (10 years) of deliveries at least
- ✓ High minimum stocks of drug substance at the manufacturing site

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

LOW

Step 2 - continued:

Drug Product & Packaging:

The drug product consists only of the drug substance, either filled into cylinders or cryogenic vessels, or directly transported via road tankers to hospital storage tanks. If filled into cylinders the cylinders can be made of aluminum or steel and are of different sizes with valves fitted to the cylinders. The packaging, ie. 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 oxygen as well as for the drug product filling equipment has historically been extremely 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. In case of liquid oxygen, the gas is stored at very low temperatures in insulated vessels or storage tanks, which are also independent from electricity supply. When stored as a liquid the product is affected by evaporation, therefore making the storage period lower, depending on the vessel / storage tank size.
The drug product is generally manufactured via the vaporisation of liquid oxygen into its gaseous form and then the compression and filling of the gaseous oxygen into cylinders, making the manufacturing process extremely stable and consistent. In the case of liquid oxygen filling, this consists of a transfer of liquid oxygen from one storage tank or vessel to another, equally 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 rejected batch 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 or road tanker 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 made from ambient air – readily available
- ✓ Reusable packages (min. 10 years) and reliable packaging manufacturers
- ✓ Aging of equipment negligible
- ✓ High quality products, < 0,1% 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. Distribution to hospitals is under the responsibility of the Marketing Authorization Holders. The tanks at the hospital sites are generally remotely monitored and therefore the deliveries are scheduled automatically. For cylinder product 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 Oxygen as the distribution is directly done by the Marketing Authorization Holders.

➔ ***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 B** 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 oxygen supply chain and all associated risks and concluded that for medicinal oxygen **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 medicinal oxygen should be assessed as **not** required to be included in the "Union list of critical medicines" as the security in supply and prevention of shortages is assured.
EIGA again wishes to emphasize that in Europe, and as confirmed to the European Medicines Agency (EMA), during the COVID-19 pandemic our members confirmed that at no time was there a shortage of oxygen to patients in healthcare facilities or for home oxygen use. Due to the significant increase in demand for oxygen during the COVID-19 pandemic, some issues were encountered in relation to equipment and manpower, but these were resolved via regulatory flexibilities agreed to by national authorities.

EIGA recommends that this SHORTAGE PREVENTION PLAN (SPP) can be used for all EIGA member companies.

Note: for some exceptional cases (e.g. remote locations), where some hazards may not have been covered by the current document it may be appropriate to amend the assessment accordingly.