TECHNICAL BULLETIN

Prepared by WG-7 TB 053/24 – May 2024

Shortage Prevention Plan

Air, Medicinal and Air, Synthetic Medicinal

Introduction:

This document covers the medicinal products Air compressed and Air synthetic (hereinafter commonly referred to as “products”). The products have individual Ph.Eur. monographs with different quality attributes because of the different manufacturing processes: 1238 for Air, medicinal and 1684 for Air, synthetic medicinal. Both products are equivalent and are commonly used worldwide for many years.

Products are supplied to healthcare facilities as a licensed medicinal product in defined packages (gas cylinders and cylinder bundles) and usually distributed via the medical gas pipeline supply system owned and operated by the healthcare facility.

In large healthcare facilities sometimes an on-site production of air is carried out under the supervision and responsibility of the hospital pharmacist. Such production (of an unlicensed “magistral formula”) is limited to the needs of the hospital itself and cannot cover the needs of other healthcare facilities.

EIGA emphasizes that in Europe at no time was there a shortage of air, medicinal and air, synthetic medicinal to patients in healthcare facilities or at home.

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.
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.

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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 products:

- Prevention of hypoxia where treatment with atmospheric air is indicated.
- Carrier gas for volatile anaesthetics for anaesthesia.

Therefore, the assessment is that Air 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 the products. 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

MEDIUM: Limited controls exist for a hazard

HIGH: No controls exist for a hazard

Drug Substance:

For air, medicinal synthetic (Ph. Eur. Monograph 1684), the components are oxygen (drug substance) and nitrogen (excipient), both 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 and nitrogen than is required for the manufacture of air, medicinal synthetic to cover patients use across Europe, with only a small percentage of oxygen and nitrogen produced at an ASU being used for healthcare purposes. Manufacturing of oxygen and nitrogen 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. For air, medicinal (Ph. Eur. Monograph 1238) the drug substance is atmospheric air, which is compressed and purified before being filled into gas cylinders.

- ✓ 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 of the drug substance and the excipient (in the case of air, synthetic medicinal: oxygen and nitrogen) or of the drug substance (ambient air in case of air, medicinal), filled into cylinders or cylinder bundles. Cylinders can be made of aluminum or steel and are of different sizes with valves fitted to the cylinders. 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 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 the case of air, synthetic medicinal, the drug product is obtained by means of a mere transfer of gas from a cryogenic storage (a sequential transfer or blending and compression), while for air, medicinal is a mere compression and purification of ambient air into the cylinders, making both manufacturing processes 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.

- ✓ Simple production process
- ✓ In the case of air, synthetic medicinal, drug product consisting of one drug substance and one excipient, both stocks are usually quite large; in the case of air medicinal, the only component is ambient air.
- ✓ 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.
Distribution to hospitals is under the responsibility of the Marketing Authorization Holders.

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 products 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 air, medicinal and air, synthetic medicinal supply chain and all associated risks and concluded that for the products **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 air 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 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.

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