TECHNICAL BULLETIN

Prepared by WG-7

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Shortage Prevention Plan

Medicinal Carbon Dioxide / Carbon Dioxide Mixtures

Introduction:

This document covers the medicinal product carbon dioxide (CO_2) with an assay of more than 99,5% (V/V) and carbon dioxide mixtures with concentrations up to 5% of carbon dioxide in oxygen (O_2). The active substance in these mixtures is carbon dioxide.

Carbon dioxide can be produced via a number of different processes, often as a by-product of many different natural and chemical processing mechanisms. All sources of carbon dioxide used as a medical gas must be qualified in order to ensure that the impurity profile is understood and has been appropriately assessed to ensure its suitability as a medicinal product.

Carbon dioxide is a liquefied gas and as such is filled into steel or aluminium cylinders to a pre-determined target weight. Carbon dioxide mixtures involve a further process of mixing with oxygen either in the cylinder or as a pre-mix before being compressed into steel or aluminium cylinders.

Carbon dioxide is typically used as an insufflation gas for surgical and diagnostic endoscopic procedures, in its liquid form as a cooling/freezing media for topical cryotherapy or mixed with oxygen (typically 5% CO_2 / 95% O_2) and administered to patients for the stimulation of spontaneous respiration. Additionally, it can be used to treat skin circulatory disorders, in so called CO_2 baths, where patients are placed into full body bags infused with CO_2 at an optimal concentration.

Usually, carbon dioxide/carbon dioxide mixtures are supplied to healthcare facilities as licensed medicinal products (or in some countries carbon dioxide is classified as a medical device) in defined packages as a liquefied gas or gaseous mixture in aluminum or steel cylinders.

EIGA emphasizes that in Europe at no time was there a shortage of medicinal carbon dioxide / carbon dioxide 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

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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 carbon dioxide/carbon dioxide mixtures are:

Carbon dioxide, used in combination with other medical devices for the following purposes:

- As an insufflation gas for surgical and diagnostic endoscopic procedures through body orifices and artificial orifices
- As a cooling/freezing media for topical cryotherapy
- as carbon dioxide baths, gas baths, spray baths to treat certain (arterial) circulatory disorders in the limbs, trophic skin ulcers, venous ulcers (wounds that heal poorly, especially on the lower legs and feet) and chronic venous insufficiency

Carbon dioxide mixtures:

- Typically, not more than 5% in O_2 for stimulation of spontaneous respiration during normobaric administration of oxygen for the treatment of CO-intoxication

Therefore, the assessment is that carbon dioxide/carbon dioxide mixtures are ‘other indications’.

In the assessment of alternatives, the outcome is that there are many “Exact products available”. Although the status of CO_2 and its mixtures is not always the same within Europe, where it is registered as a medicinal product there are many MAHs and where it is registered as a medical device there are many manufacturers/distributors, 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.**

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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 carbon dioxide drug substance for the carbon dioxide/carbon dioxide mixtures is manufactured via a number of different processes, often as a by-product of many different natural and chemical processing mechanisms. The main uses of carbon dioxide are for non-medical applications, such as in the food and beverage industries, with only small amounts of carbon dioxide being used for medicinal purposes.
There are several manufacturing plants for carbon dioxide for medicinal purposes within the European Union that can produce more carbon dioxide than is 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 by road via road tankers. 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.

➔ ***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 or of the drug substance and oxygen (with the oxygen 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 filling the drug substance into cylinders or by mixing the carbon dioxide with oxygen and filling 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 or road tanker is the final packaging with no relabeling performed.

- ✓ Simple production process
- ✓ Drug product consist of only the drug substance, drug substance stock 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 carbon dioxide/carbon dioxide 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:

		Likelihood of Shortage		
		High	Moderate	Low
Therapeutic Use & Consequneces if Product is not Available	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 carbon dioxide/carbon dioxide mixtures supply chain and all associated risks and concluded that for medicinal carbon dioxide/carbon dioxide 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 carbon dioxide and carbon dioxide 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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