

Shortage Prevention Plan

Medicinal Carbon Dioxide / Carbon Dioxide Mixtures

Introduction:

This document covers the medicinal product carbon dioxide (CO₂) with an assay of more than 99,5% (V/V) and carbon dioxide mixtures with concentrations up to 5% of carbon dioxide in oxygen (O₂). 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% CO₂ / 95% O₂) and administered to patients for the stimulation of spontaneous respiration. Additionally, it can be used to treat skin circulatory disorders, in so called CO₂ baths, where patients are placed into full body bags infused with CO₂ 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 O₂ 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'.

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In the assessment of alternatives, the outcome is that there are many “Exact products available”. Although the status of CO₂ 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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