

General Safety and Performance Requirements of Medical Device Regulation applied to Carbon Dioxide

Introduction

The Medical Device Regulation (MDR) has been in force since 26th May 2021 and has introduced in Annex I, i.e. in the General Safety and Performance Requirements (GSPR), both new requirements and changes, compared to the list of essential requirements of Dir. 93/42/EEC Annex I.

This Technical Bulletin provides guidance on the interpretation of the GSPR in annex I of the MDR, when applied to gaseous Carbon Dioxide as a medical device, i.e. for insufflation, and to provide recommendations on how to implement them.

The same list of requirements may be used for other applications of CO₂ when classified as a medical device, provided that detailed purposes are described and justified by each manufacturer according to their clinical evaluation in their technical documentation.

Summary

The Technical Bulletin analyses all the requirements, dividing them between those certainly not applicable and those certainly applicable. Moreover, it includes justification when the applicability needs to be clarified, with references to applicable standards, general guidance documents and other EIGA documents that may be used to support the manufacturers.

This Technical Bulletin does not cover national regulations that may apply.

Table reading guidance

Table 1 – Applicable requirements and requirements that need justifications:

- Column 1 MDR requirement is reported with text
- Column 2 reference to standards, including in some cases specific points.
- Column 3 applicability statement with yes or no
- Column 4 EIGA members interpretation and/or recommendation is given. It reflects the current status of understanding and can be subject to changes.

Table 2 - Not applicable requirements

- Column 1 MDR requirements are listed as points grouped by justification
- Column 2 – justification

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MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	applicable standards - general guide - specific points and subpoints (related MDR)	applicable?	Response
I - GENERAL REQUIREMENTS	title	title	title
1. Devices shall achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose . They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art .	ISO 14971 (5.2-5.3) Note: to date an ISO 14971:2019 is the state of the art, references here have been made to this version.	Y	The intended purpose of CO ₂ (gaseous state) is for example to create a space by insufflation. Detailed purposes shall be described by each manufacturer according to their clinical evaluation. See also EIGA TB 30 for potential purposes. The patient population refers to the detailed purposes. Specific exclusions shall be described. The users of the CO ₂ is the surgeon, the user of the cylinder (transport, preparation...) may also be a technician. The performances required by the CO ₂ : is linked to the quality of CO ₂ (the quality shall not be less than PhEUR one), and the conditions of the package (i.e. cylinder+valve functionality and safety), and the availability of the gas in the package. The risk/benefit ratio shall be addressed by the risk management plan. The validation of the performances for CO ₂ is the validation of the filling process where the quality of the gas is verified, the availability of the gas in the package (quantity per package) is verified and the safety and functionality of the cylinder and valve as well.
2. The requirements in this annex to reduce risks as far as possible mean reduce risks as far as possible without adversely affecting the risk benefit ratio.	ISO 14971 (7.4; 8)	Y	The risk management conclusions shall define if the benefit overcome the risk. The risk management plan and conclusions shall be drawn up according to ISO 14971.
3. Manufacturer shall establish, implement, document and maintain a risk management system.	ISO 14971 (4)	Y	Each manufacturer shall have a risk management system in place following the ISO 14971 (or GMP). The system shall be documented.

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3.(continue) Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic update. In carrying out risk management manufacturers shall:	ISO 14971 (4.1;4.2) ISO 13485 (5.6)	Y	The procedures for design and development, vigilance and post market surveillance shall include the requirement of risk management plan re-evaluation according to the outcomes of their reports, whether periodic (such as for PMS) or on single event (such as for vigilance).
3. (a) establish and document a risk management plan for each device;	ISO 14971 (4.4)	Y	The risk management plan is defined as part of the technical documentation of each device or device family (=1 plan for 1 technical documentation file).
3. (b) identify and analyse the known and foreseeable hazards associated with each device;	ISO 14971 (5.4)	Y	Some of the hazards are identified though the analysis of the applicable GSPRs below.
3. (c) estimate and evaluate the associated risks occurring during the intended use and during reasonably foreseeable misuse;	ISO 14971(5.2)	Y	Each manufacturer shall evaluate associated risks according to the package and the intended uses specified in the clinical evaluation.
3. (d) eliminate or control these risks according to the requirements of Section (GSPR) 4;	GSPR No. 4; ISO 14971 (7)	Y	The risk management plan defines the measures for risks reduction, such as controls during production.
3. (e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit risk ratio and risk acceptability; and	ISO 14971 (10); MDGC 2020-7	Y	Each manufacturer shall review information deriving from production (such as nonconformities, out of spec, ...) and from post market surveillance information (such as feedback from customers and vigilance cases). These may affect the frequency or estimated severity of the risks.
3. (f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.	ISO 14971 (10.4); ISO TR 20416 (5.8;6.2)	Y	The procedure for post market surveillance shall include the requirement that the PMS reports evaluates the need of risk assessment re-evaluation.

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4. risk control measures adopted by the manufacturer for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, the manufacturer shall manage the risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, the manufacturer shall apply the following principles in the priority order listed:	ISO 14971 (4.2,4.4,6,7,8)	Y	In the risk assessment file for each risk after the application of the control measures the acceptability of each risk shall be defined. While the conclusions shall define if the benefit overcome the overall residual risk.
4. (a) eliminate or reduce risks as far as possible through safe design and manufacture;	ISO 14971 (7.1a)	Y	The risk management plan shall describe the 3 criteria.
4. (b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and	ISO 14971 (7.1b)	Y	The risk management plan shall describe the 3 criteria.
4. (c) provide information for safety (warnings / precautions / contraindications) and, where appropriate, training to users.	ISO 14971 (7.1c) EN ISO 15223-1	Y	The risk management plan shall describe the 3 criteria.

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4. (continue) The manufacturer shall inform users of any residual risks.	ISO 14971 (8 2nd par.)	Y	When there is a residual risk that cannot be eliminated, the users are informed through leaflets (i.e. instruction for use). The risks to be included for CO₂ are related to the safety of "handling the cylinder" and the risks related to the CO₂ when it is inside the patient, and the risk of interface with the other device (e.g., Use of pressure regulator, valve connection). The risk to be excluded are those related to the other devices. Only the general information that the user shall check for the compatibility between the devices.
5. In eliminating or reducing risks related to use error the manufacturer shall: (a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and	ISO 14971 (5.2, 5.3, 5.4, 7)	Y	The design applies the standards for the valve connection which is the only manipulated part of the device + its containment.
5. (b) give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).	ISO 14971 (5.2, 5.3, 5.4) IEC 62366 (5.1; 5.2;5.3; 5.4; 5.6)	Y	The target users are: - the physician for the destination of use of CO₂ - the technician within the hospital or nurses for the preparation for use (i.e. connection with other devices, opening of the valve), and after use (close, disconnect). The technical documentation shall include a usability evaluation file for the preparation for use and disconnection.

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6. The characteristics and performances of the device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.	ISO 14971 (5.2, 5.3, 5.4)	Y	The lifetime of the gas is linked to the stability information provided in the technical documentation. Maintenance is not required to the user, but the empty cylinder need to be verified for its performance before re-filling. Instruction for these pre-production checks needs to be included in the technical documentation.
7. Devices shall be designed, manufactured and packaged in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.		Y	The temperature range for safe CO ₂ storage is derived by the MSDS. For the transport the valve shall be protected by a cap. Only PIN index valves do not require a cap for transport. The cylinders and valve are approved according to T-PED Directive. The transport between the gas supplier and the customer is regulated by ADR. EIGA references for transport and storage at the customers' site is EIGA SL 08 Detailed description of the procedures in use and the information to customers shall be provided in the technical documentation.
8. All known and foreseeable risks , and any undesirable side-effects, shall be minimised(1) and be acceptable when weighed against the evaluated benefits to the patient and/or user of the achieved performance of the device during normal conditions of use.	ISO 14971 (6,7,8)	Y	Foreseeable risks and side effects shall be included in the risk assessment and as such weighted if acceptable.

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II- REQUIREMENTS REGARDING DESIGN AND MANUFACTURING (MDR)	title	title	Title
10. Chemical, physical and biological properties	title	title	Title
10.1 Devices shall be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Chapter I 'General Requirements'. Particular attention shall be paid to:		Y	See following GSPRs answers.
10.1 (a) the choice of materials and substances used, particularly as regards toxicity and, where appropriate, flammability;	ECHA CO2 toxicological profile	Y	The toxicity profile of CO ₂ is available on ECHA as well as the MSDS.
10.1 (b) the compatibility between the materials and substances used and biological tissues, cells, and body fluids taking account of the intended purpose of the device and, where relevant, absorption, distribution, metabolism and excretion ;	ISO 10993 series (direct or indirect contact with: — the patient's body during intended use; — the user's body)	Y	The compatibility between the cylinder and the valve materials with the gas is reported by the ISO 11114-1 for metallic materials and 11114-2 for non-metallic materials (i.e. gaskets). The bio-compatibility between the gas and the body shall be described in the biocompatibility report part of the technical documentation.
10.1 (d) the impact of processes on material properties;		NA needs justification	There are no risks related to the materials during production of the device.
10.1 (e) where appropriate, the results of biophysical or modelling research whose validity has been demonstrated beforehand;		NA needs justification	Biophysical or modelling research are not applicable to CO ₂ .
10.1 (f) the mechanical properties of the materials used, reflecting, where appropriate, matters such as strength, ductility, fracture resistance, wear resistance and fatigue resistance;		Y	Cylinder and valve are purchased T-PED approved.
10.1 (g) surface properties; and		NA	The cylinders do not require specific internal surface treatments.

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		needs justification	
10.1 (h) the confirmation that the device meets any defined chemical and/or physical specifications		Y	The CO ₂ shall conform to the PhEur specification as a minimum (or the specification identified by the manufacturer), the manufacturing process shall identify how to verify before release that the product is conform.
10.2 Devices shall be designed, manufactured and packaged in such a way as to minimise the risk posed by contaminants and residues to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage and use of the devices. Particular attention shall be paid to tissues exposed and to the duration and frequency of exposure.		Y	Risks related to manufacturing, transport and storage shall include evaluation of residues and contaminants. The EIGA DOC 62 identifies all possible risks to be considered and how to minimise them. To be identified in the risk assessment.
10.3 Devices shall be designed and manufactured in such a way that they can be used safely with the materials and substances, including gases, with which they enter into contact during their intended use ; if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these medicinal products and that both the performance of the medicinal products and of the devices are maintained in accordance with their respective indications and intended use.		Y	The device is a gas itself. Nevertheless, the instruction for use shall inform about the need of compatibility with CO ₂ of other devices used in combination.
10.4. Substances	Title	Title	Title

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10.4.1 Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products, processing residues, that may be released from the device.		Y	This risk is applicable during the assembly of valve with cylinder; therefore, it has to be considered for the approval of test shops, or when the valve is assembled by the gas manufacturer. The risk of residues deriving from previous fillings shall be considered in the risk management. the risk of external contamination shall be considered as well. For external contamination see EIGA DOC 222.
10.4.1 Devices, or those parts thereof or those materials used therein that:		Y	See subpoints below.
10.4.1 1st — are invasive and to come into direct contact with the human body, shall only contain the following substances in a concentration above 0.1% weight by weight (w/w) when justified pursuant to Section 10.4.2; or		NA needs justification	CO ₂ is not by itself a CMR or endocrine disruptor. EIGA DOC 216 provides documented evidence that traces of lead is found in the gas administered to the patient in a level lower than the safety limits defined in the ICH Q3D, and also less than 0.1% w/w. This document considers as the worst-case scenario (O ₂ 10800 L as acute treatment, and 7.5 L/min over 24 h), however this could include also the use of CO ₂ for laparoscopy/Endoscopy applications since: the use of CO ₂ for the first insufflation is about 4–6 litre min ⁻¹ to a pressure of 10–20 mm Hg. Then the pneumoperitoneum is maintained by a constant gas flow of 200–400 ml min ⁻¹ .
10.4.1. 2nd — (re)administer medicines, body liquids or other substances, including gases, to/from the body, shall only contain the following substances in a concentration above 0.1% weight by weight (w/w) when justified pursuant to Section 10.4.2; or		NA needs justification	The device is not intended to (re)administer medicines, body liquids or other substances, including gases, to/from the body.
10.4.1. 3rd — transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body, shall only contain the following substances in a concentration above 0.1%		Y	The following considerations shall be made on the container closure system (cylinder + valve) used to transport and store the CO ₂ : Within the high-pressure gas industry, the most suitable material used for cylinder valves has been found to be high tensile brass which has more than 0.1% of lead present, required for mechanical

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weight by weight (w/w) when justified pursuant to Section 10.4.2:			strength of the brass and allows it to be machined accurately. EIGA DOC 216 provides documented evidence that traces of lead is found in the gas administered to the patient in a level lower than the safety limits defined in the ICH Q3D, and also less than 0.1%. This document considers as the worst-case scenario (O ₂ 10800 L as acute treatment, and 7.5 L/min over 24 h), however this could include also the use of CO ₂ for laparoscopy/Endoscopy applications since: the use of CO ₂ for the first insufflation is about 4–6 litre min ⁻¹ to a pressure of 10–20 mm Hg. Then the pneumoperitoneum is maintained by a constant gas flow of 200–400 ml min ⁻¹ .
10.4.1 (a) substances which are carcinogenic, mutagenic or toxic to reproduction of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament or	ECHA CO ₂ toxicological profile	NA needs justification	CO ₂ is not by itself a CMR or endocrine disruptor. Data on CO ₂ properties are available in the ECHA toxicological profile.
10.4.1 (b) substances having endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council ² or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council ³ , in accordance with the criteria that are relevant to human	ECHA CO ₂ toxicological profile	NA needs justification	CO ₂ is not by itself a CMR or endocrine disruptor. Data on CO ₂ properties are available in the ECHA toxicological profile.

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