TECHNICAL BULLETIN

Prepared by WG-15 TB 52/24 – April 2024

General Safety and Performance Requirements of Medical Device Regulation applied to Argon

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.

The objective of this Technical Bulletin is to give guidance on the interpretation of the GSPR in Annex I of the MDR, when applied to gaseous Argon as a medical device such as intended for plasma coagulation or cryoablation, and to provide implementation recommendations.

Summary

This Technical Bulletin analyses all the requirements and identifies whether they are applicable or not applicable including any justification where needed.
It also includes 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.

Note: It reflects the current status of understanding.

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 Argon (AR) is used at gas state in surgery to generate plasma or for cryoablation. More detailed purposes shall be described by each manufacturer according to their Clinical evaluation. The patient population refers to the detailed purposes. Specific exclusions shall be described. The users of the Argon is the surgeon, the user of the cylinder (transport, preparation...) may also be a technician. The performances required by the Argon: is linked to the quality of Argon (the quality shall be in compliance with internal product specification identified by the manufacturer), 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 Ar 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 risks that cannot be eliminated, the users are informed through leaflets (i.e. instruction for use). The risks to be included for Ar are related to the safety of "handling the cylinder" and the risks related to the Ar 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 Ar - 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 Ar storage is derived by the MSDS. For the transport the valve shall be protected by a cap. 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.
II- REQUIREMENTS REGARDING DESIGN AND MANUFACTURING (MDR)	**title**	**title**	**Title**
10. Chemical, physical and biological properties	**title**	**title**	**Title**

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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 Argon toxicological profile	Y	for the point 10.1a the toxicity profile of Argon 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 biocompatibility 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 Argon.
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 needs justification	The cylinders do not require specific internal surface treatments.

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10.1 (h) the confirmation that the device meets any defined chemical and/or physical specifications		Y	The Ar shall be in compliance with internal product 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 contaminates. 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 Ar 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	Ar 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 (O2 10800 L as acute treatment, and 7.5 L/min over 24 h), however this could include also the use of Ar for Cryoablation/plasma coagulation applications.
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% weight by weight (w/w) when justified		Y	The following considerations shall be made on the container closure system (cylinder + valve) used to transport and store the Ar: 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 strength of the brass and allows it to be machined accurately. EIGA DOC 216

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pursuant to Section 10.4.2:			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 (O2 10800 L as acute treatment, and 7.5 L/min over 24 h), however this could include also the use of Argon for Cryoablation/plasma coagulation applications.
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 Argon toxicological profile	NA needs justification	Ar is not by itself a CMR or endocrine disruptor. Data on Ar 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 Council2 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 Council3, in accordance with the criteria that are relevant to human	ECHA Argon toxicological profile	NA needs justification	Ar is not by itself a CMR or endocrine disruptor. Data on Ar properties are available in the ECHA toxicological profile.

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10.4.2. Justification regarding the presence of CMR substances and/ or endocrine disruptors. The justification for the presence of such substances shall be based upon: (a) an analysis and estimation of potential patient or user exposure to the substance; (b) an analysis of possible alternative substances, materials or designs, including, when available, information about independent research, peer reviewed studies, scientific opinions from relevant Scientific Committees and an analysis of the availability of such alternatives; (c) argumentation why possible substance and/ or material substitutes or design changes, if available, are inappropriate to maintain the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or nursing women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials; and (d) Where applicable and available, the latest relevant Scientific Committee guidelines in accordance with Sections 10.4.3. and 10.4.4.		Y	See statement at 10.4.1 3rd indent.

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10.4.3. Guidelines on phthalates For the purposes of Section 10.4., the Commission shall, as soon as possible and by K 26 May 2016provide the relevant scientific committee with a mandate to prepare guidelines that shall be ready before K 26 May 2020. The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of phthalates which belong to either of the groups of substances referred to in points (a) and (b) of Section 10.4.1. The benefit risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments. When deemed appropriate on the basis of the latest scientific evidence, but at least every five years, the guidelines shall be updated.		NA needs justification	Non-metallic components of the container closure system may include phthalates as plasticisers, however these are generally not within the gas pathways that delivers gas to the patient. They are generally used to seal valve components to prevent leakages.
10.4.5 Labelling. Where devices, parts thereof or materials used therein as referred to in Section 10.4.1. contain substances referred to in points (a) or (b) of Section 10.4.1. in a concentration above 0,1 % weight by weight (w/w), the presence of those substances shall be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging, with the list of such substances.		Y	The information on the presence of lead in the valve shall be disclosed.

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10.4.2 (continue) If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures shall be given in the instructions for use.		Y	The information about no residual risks due to conclusions of EIGA DOC 216 shall be included.
10.5. Devices shall be designed and manufactured in such a way as to reduce as far as possible risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.		Y	The use of Residual pressure valves (RPV) or other methods to avoid ingress of substances into the device shall be considered in the risk assessment.
10.6. Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body unless they come into contact with the intact skin only. Special attention shall be given to nanomaterials.		NA needs justification	No nanomaterials are present. For other residues see 10.2.
11.Infection and microbial contamination	**title**	**title**	**Title**
11.1. Devices and manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, **where applicable, other persons.**		NA needs justification	The gas which is the only part of the device in contact with the patient cannot be contaminated by an external source. Internal biological contamination of cylinders and why it is not considered a hazard is defined in the EIGA DOC 232.

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11.1 (d) prevent microbial contamination of the device or its content such as specimens or fluids			
11.2. Where necessary devices shall be designed to facilitate their safe cleaning, disinfection, and/or re-sterilisation.		Y	A Cleaning procedure for valve connection shall be identified.
12. Devices incorporating a substance considered to be a medicinal product and devices that are composed of substances or combination of substances that are absorbed by or locally dispersed in the human body	**title**	**title**	**title**
12.1 In the case of devices referred to in the first subparagraph of Article 1(8), the quality, safety and usefulness of the substance which, if used separately, would be considered to be a medicinal product within the meaning of point (2) of Article 1 of Directive 2001/83/EC, shall be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC, as required by the applicable conformity assessment procedure under this Regulation		NA needs justification	Argon is not a medicinal product on its own, it could be used in mixtures as a medicinal product.

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12.2. Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body, and that are absorbed by or locally dispersed in the human body shall comply, where applicable and in a manner limited to the aspects not covered by this Regulation, with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as required by the applicable conformity assessment procedure under this Regulation		NA needs justification	Argon is not considered to be absorbed or locally dispersed for achieving its intended purpose.
14. Construction of devices and interaction with their environment	**title**	**title**	**Title**
14.1. If the device is intended for use in combination with other devices or equipment the whole combination, including the connection system shall be safe and shall not impair the specified performance of the devices. Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instructions for use. **Connections which the user has to handle, such as fluid, gas transfer, electrical or mechanical coupling, shall be designed and constructed in such a way as to avoid**		Y	Valve connections are selected according to national or international standards, depending on the country of distribution. National or international standards consider a different design according to the gas type to avoid misconnection.

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misconnection.			
14.2. Devices shall be designed and manufactured in such a way as to remove or reduce as far as possible: (a) the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features;		Y	The cylinder and valve must be selected as appropriate for the gas, the maximum filling pressure shall be considered.
14.2 (b) risks connected with reasonably foreseeable **external influences** or environmental conditions, such as magnetic fields, external electrical **and electromagnetic** effects, electrostatic discharge, **radiation associated with diagnostic or therapeutic procedures**, pressure, **humidity**, temperature, variations in pressure and acceleration or **radio signal interferences**;		Y	Hazards that are applicable to the Argon cylinders are: pressure and temperature variations. These shall be addressed in the risk assessment
14.2 (c) the risks associated with <u>the use</u> of the device when it comes into contact with materials, liquids, and substances,		Y	The compatibility with Argon shall be considered for devices used in combination with Argon.

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including gases, to which it is exposed during normal conditions of use;			
14.2 (e) the risks of accidental ingress of substances into the device		Y	See answer to 10.4
14.2 (f) the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given;		NA needs justification	No interferences has been to date found for the use of Argon in plasma coagulation procedures.
14.2 (g) risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.		Y	Maintenance is not appliable to the gas. The risks are related to the aging of the cylinder which has to be periodically re-tested, and to potential valve damages during transport. During filling process the valve functionality is tested.
14.3. Devices shall be designed and manufactured in such a way as to minimise the risks of fire or explosion during normal use and in single fault condition. Particular attention shall be paid to devices whose intended use includes exposure to or use in association with flammable or explosive substances or substances which could cause combustion.		NA needs justification	Argon is not flammable thus it is not applicable. Risks related to pressure have been considered in 14.2(b)
14.4. Devices shall be designed and manufactured in such a way that adjustment, calibration, and maintenance can be done safely and effectively.		NA needs justification	Neither calibration nor maintenance are required for the user. The cylinder needs to undergo to periodic tests according to the T-PED/ADR requirements. These tests are responsibility of the cylinder owner and carried out in specialized centres.
14.5. Devices that are intended to be operated together with other devices or products shall be designed and manufactured in such a way that the interoperability and compatibility are reliable and safe.		Y	See answer to 14.1.

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14.7. Devices shall be designed and manufactured in such a way as to facilitate the safe disposal of the device and/or related waste substances by the user, patient or other person. To that end, manufacturers shall investigate and test procedures and measures by which their devices can be safely disposed after use. Such procedures shall be described in the instructions for use.	Table C.2 ISO 14971	Y	Disposal of the cylinder shall be carried out by the cylinder owner when the periodic inspection fails. Gas disposal is not applicable: the cylinder has to be sent back to the gas manufacturer for refilling when empty or not used.
18. Active devices and devices connected to them	**title**	**title**	**title**
18.1. For non - implantable active devices, in the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks.		NA needs justification	Argon during its intended use cannot undergo to a single fault condition.
18.2. Devices where the safety of the patients depends on an internal power supply shall be equipped with a means of determining the state of the power supply **and an appropriate warning or indication if, or if necessary before, the capacity of the power supply becomes critical.**		NA needs justification	No internal power supply is applicable to Argon.
18.3. Devices where the safety of the patients depends on an external power supply shall include an alarm system to signal any power failure.	Table C.2 ISO 14971	NA needs justification	No external power supply is applicable to Argon.
20. Protection against mechanical and thermal risks	**title**	**title**	**title**
20.1. Devices shall be designed and manufactured in such a way as to protect the		Y	The cylinder must be protected from falls. The risk shall be evaluated in the risk assessment.

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patient and user against mechanical risks connected with, for example, resistance to movement, instability and moving parts.			
20.2. Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.		NA needs justification	The cylinder and valve do not create vibration when Argon is extracted for its use.
20.3. Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.		NA needs justification	The noise emitted when opening the valve it is not relevant.
20.4. Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user **or other person** has to handle shall be designed and constructed in such a way as to minimise all possible risks.	ISO 5145 N°17 NBN 226 DIN 477 AFNOR E 29-650 UNI 11144 EN ISO 407	Y	The valve connection shall be selected among the national or international standards for medical gas connection, according to the country of distribution some examples are: NBN 226 - W 21,8 x 1/14 DIN 477 No. 6 W 21,8 x 1/14 NF E 29-650 No. C 21,7/1,814 UNI 11144 uscita N.8 W 24,51 × $1/_{14}$" F ISO 5145 n°4

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
20.5. Errors likely to be made when fitting or refitting certain parts which could be a source of risk shall be made impossible by the design and construction of such parts or, failing this, by information given on the parts themselves and/or their housings. The same information shall be given on moving parts and/or their housings where the direction of movement needs to be known in order to avoid a risk.		NA needs justification	The only possible fitting/refitting is the use of the terminal connector of the valve, thus this GSPR is already answered above with a more specific one: see GSPR 20.4.
20.6. Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings shall not attain potentially dangerous temperatures under normal conditions of use.		NA needs justification	There are no accessible parts of the device which could attain potential dangerous temperatures.
21. Protection against the risks posed to the patient or user by supplied energy or substances	**Title**	**title**	**title**
21.1. Devices for supplying the patient with energy or substances shall be designed and constructed in such a way that **the delivered amount** can be set and maintained accurately enough **to assure** the safety of the patient and of the user.	Table C.1 ISO 14971	NA needs justification	It refers to the devices used in combination with Argon for its delivery to the patient.
21.2. Devices shall be fitted with the means of preventing and/or indicating any inadequacies in the **delivered amount of energy or substances** which could pose a danger. Devices shall incorporate suitable means to prevent, as far as possible, the accidental	Table C.1 ISO 14971	NA needs justification	It refers to the devices used in combination with Argon for its delivery to the patient.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
release of dangerous levels of energy **or substances** from an energy and/or substance source.			
21.3. The function of the controls and indicators shall be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information shall be understandable to the user and, as appropriate, the patient.	Table C.1 ISO 14971; ISO 62366-1	NA needs justification	It refers to the devices used in combination with Argon for its delivery to the patient.
III. Requirements regarding the information supplied with the device **23. Label and instructions for use (i.e. leaflet)**	**title**	**title**	**title**
23.1. General requirements regarding the information supplied by the manufacturer. Each device shall be accompanied by the information needed to identify the device and its manufacturer, and by any safety and performance information relevant to the user, **or any other person, as appropriate**. Such information may appear on the device itself, on the packaging or in the instructions for use, and shall, **if the manufacturer has a website, be made available and kept up to date on the website, taking into account the following:**		Y	All cylinders are provided with label and leaflet (i.e. Instruction for use). If the manufacturer has a website the instruction for use shall be made available and kept up to date on the website,

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.1 (a) The medium, format, content, legibility, and location of the label and instructions for use shall be appropriate to the particular device, its intended purpose and the technical knowledge, experience, education or training of the intended user(s). In particular, instructions for use shall be written in terms readily understood by the intended user and, where appropriate, supplemented with drawings and diagrams		Y	The label and instruction only possible location is on the cylinder. The user is a professional one that knows how to handle cylinders. The usability should consider the readability of instruction for use.
23.1 (b) The information required on the label shall be provided on the device itself. If this is not practicable or appropriate, some or all of the information may appear on the packaging for each unit, and/or on the packaging of multiple devices.		Y	The label is foreseen for each cylinder.
23.1 (c) Labels shall be provided in a human-readable format and may be supplemented by machine-readable information, such as radio-frequency identification ('RFID') or bar codes.		Y	The decision on the use of machine-readable information depends on each manufacturer.
23.1 (d) Instructions for use shall be provided together with devices. By way of exception, instructions for use shall not be required for class I and class IIa devices if such devices can be used safely without any such instructions and unless otherwise provided for elsewhere in this Section.		Y	Instruction for use is usually provided with each cylinder.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.1 (e) Where multiple devices are supplied to a single user and/or location, a single copy of the instructions for use may be provided if so agreed by the purchaser who in any case may request further copies to be provided free of charge.		NA needs justification	See previous point. Each manufacturer could define anyway if this clause is applicable. If so demonstration on the feasibility of the application should be available.
23.1 (f) Instructions for use may be provided to the user in non-paper format (e.g. electronic) to the extent, and only under the conditions, set out in Regulation (EU) No 207/2012 or in any subsequent implementing rules adopted pursuant to this Regulation.	Regulation (EU) No 207/2012	NA needs justification	The device is not fixed installed, implantable or standalone thus the non-paper format is not a feasible solution for Argon cylinders IFU.
23.1 (g) Residual risks which are required to be communicated to the user and/or other person shall be included as limitations, contra-indications, precautions or warnings in the information supplied by the manufacturer.		Y	Residual risks to be disclosed derive from the risk assessment, including those deriving from the clinical evaluation.
23.1 (h) Where appropriate, the information supplied by the manufacturer shall take the form of **internationally recognised** symbols. Any symbol or identification colour used shall conform to the harmonised standards or **CS**. In areas for which no harmonised standards or CS exist, the symbols and colours shall be described in the documentation supplied with the device.	ISO 7000, ISO 7010 ISO 15223-1; EN 1089-3	Y	The symbols used shall be derived from ISO 7000, ISO 7010, ISO 15223-1. The identification colour for the cylinder shoulder and the cylinder body are described by EN 1089-3. Shoulder: Dark Green (RAL 6001) Body: white (RAL 9010)
23.2. Information on the label. The label shall bear the following particulars:	**title**	**title**	**title**
23.2 (a) The name or trade name of the device.	EN ISO 15223-1 (5.1.6)	Y	

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.2 (b) the details strictly necessary for a user to identify the device, the contents of the packaging and, **where it is not obvious for the user, the intended purpose of the device;**		Y	The intended purpose shall be written in short (vs. fully required for 23.4(b)) on the label (e.g. for plasma coagulation …)
23.2 (c) the name, registered trade name or registered **trade mark(1)** of the manufacturer and the **address of its registered place of business;**	EN ISO 15223-1 (5.1.1)	Y	
23.2 (d) if the manufacturer has its registered place of business outside the Union, the name of the authorised representative and address of the registered place of business of the authorised representative;		NA needs justification	EIGA members have usually at least one EU manufacturer within each company. If not, then the EU representative shall be identified.
23.2 (f) where applicable, information labelled in accordance with Section 10.4.5		Y	See GSPR 10.4.1: Lead presence in the valve shall be disclosed.
23.2 (g) the lot number or the serial number of the device preceded by the words LOT NUMBER or SERIAL NUMBER **or an equivalent symbol, as appropriate;**	EN 15223-1 (5.1.7)	Y	Argon is managed by lot number, for which EN 15223 5.1.5 (LOT) symbol may be used
23.2 (h) the UDI carrier referred to in Article 27(4) and Part C of Annex VII;	EN ISO 15223-1 (5.7.10)	Y	The UDI carrier may be identified with the symbol EN 15223 5.7.10 (UDI)
23.2 (i) an **unambiguous** indication of the time limit for **using** or **implanting** the device safely, expressed at least in terms of year and month, where this is relevant;	EN ISO 15223-1 (5.12)	Y	The expiry date of the Argon has been defined in GSPR N. 6. The label shall report this expiry date, according to the production date of the batch. The EN 15223 symbol may be used: USE by date 5.12
23.2 (j) **where there is no indication of the date until when it may be used** safely, the date of manufacture. This date of manufacture may be included as part of the lot number or	EN ISO 15223-1 (5.1.3)	NA needs justification	The previous GSPR is used.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
serial number, provided the date is clearly identifiable;			
23.2 (k) an indication of any special storage and/or handling condition that applies		Y	This information derives from risk assessment as examples: secure gas cylinders, keep in a ventilated room…
23.2 (q) an indication that the device is a medical device.	EN ISO 15223-1 (5.7.7)	Y	The ISO 15223 symbol 5.7.7 may be used.
23.2 (r) in the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body, the overall qualitative composition of the device and quantitative information on the main constituent or constituents responsible for achieving the principal intended action;		NA needs justification	See GSPR No. 12.2.
23.4. Information in the instructions for use (IFU)	**title**	**title**	**title**
The instructions for use shall contain the following particulars: (a) the particulars referred to in points (a), (c), (e), (f), (k), (l), (n) and (r) of Section 23.2;		Y	The points a), c), k) are applicable.
23.4 (b) the device's intended purpose **with a clear specification of indications, contra-indications, the patient target group or groups, and of the intended users, as appropriate;**		Y	The intended purpose shall be fully described (vs. short required for 23.2(b)). Indication, contraindication etc. shall match the Clinical evaluation content.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.4 (c) where applicable, a specification of the clinical benefits to be expected.		Y	It shall match the clinical evaluation content.
23.4 (d) where applicable, links to the summary of safety and clinical performance referred to in Article 32;		NA needs justification	Article 32 does not apply to Argon.
23.4 (e) the performance characteristics of the device;		Y	It shall be conform to what indicated in the technical documentation (part 1).
23.4 (f) where applicable, information allowing the healthcare professional to verify if the device is suitable and select the corresponding software and accessories;		Y	It should be considered information on how to select the correct valve connection.
23.4 (g) any **residual risks, contra-indications** and any undesirable side-effects, **including information to be conveyed to the patient in this regard;**		Y	It shall match the clinical evaluation content.
23.4 (h) **specifications the user requires to use the device appropriately, e.g. if the device has a measuring function**, the degree of accuracy claimed for it;		Y	Information to use appropriately the device are deriving from the risk assessment (e.g. pressure delivered, how to check the residual amount of gas)
23.4 (i) details of any **preparatory** treatment or handling of the device before it is ready for use or during its use, such as sterilisation, final assembly, calibration, etc., **including the levels of disinfection required to ensure patient safety and all available methods for achieving those levels of disinfection;**		Y	Information to prepare the cylinder for its use are deriving from risk assessment (e.g. how to connect the cylinder, how to open the valve…)
23.4 (j) any requirements for special facilities, or special training, or particular qualifications of the device user and/or other persons;		Y	The user for the device preparation shall be familiar with the use of a cylinder. The user of the gas shall be a trained physician for the application indicated as intended purpose.

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23.4 (k) the information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant		Y	How to check if the cylinder is appropriately connected to the downstream devices as per results of the risk assessment.
– details of the nature, and frequency, of preventive and regular maintenance, and of any preparatory cleaning or disinfection,		Y	Details on how to clean the external surface of the cylinder or valve shall be suppled.
– identification of any consumable components and how to replace them,		NA needs justification	No consumables components are foreseen for the cylinder.
– information on any necessary calibration to ensure that the device operates properly and safely during its intended lifetime, and		NA needs justification	No calibration is needed.
– methods for eliminating the risks encountered by persons involved in installing, calibrating or servicing devices;		Y	Information on how to connect the cylinder and open the valve safely shall be included.
23.4 (s) 3rd — warnings, precautions and/or measures to be taken as regards the risks of interference posed by the reasonably foreseeable presence of the device during specific diagnostic investigations, evaluations, or therapeutic treatment or other procedures such as electromagnetic interference emitted by the device affecting other equipment.		NA needs justification	See GSPR 11.2 c)

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.4 (n) if the device is reusable, information on the appropriate processes for allowing reuse, including cleaning, disinfection, packaging and, where appropriate, the **validated** method of re- sterilisation **appropriate to the Member State or Member States in which the device has been placed on the market. Information shall be provided to identify when the device should no longer be reused, e.g. signs of material degradation or the maximum number of allowable reuses;**		NA needs justification	The content could be used until the cylinder is empty. The cylinder itself is reusable, however the empty cylinder shall be re-filled by the manufacturer, and not by the user therefore information on its reuse is not applicable for the device.
23.4 (q) for devices intended for use together with other devices and/or general-purpose equipment: – information to identify such devices or equipment, in order to obtain a safe combination, and/or **– information on any known restrictions to combinations of devices and equipment;**		Y	The device shall be used with equipment intended for use with Argon.
23.4 (s) **information that allows the user and/or patient to be informed of any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device (1)**. That information shall, where relevant, allow the user to brief the patient about any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. The information shall cover, where appropriate:		Y	See subpoints below.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.4 (s) 1st — **warnings (1)**, precautions **and/or measures(2)** to be taken in the event of **malfunction of the device(3)** or changes in its performance **that may affect safety(4),**		Y	These warnings are to be derived from the risk assessment.
23.4 (s) 2nd — **warnings**, precautions and/or **measures** to be taken as regards the exposure to reasonably foreseeable **external influences** or environmental conditions, such as magnetic fields, external electrical and **electromagnetic effects**, electrostatic discharge, **radiation associated** with **diagnostic or therapeutic procedure**s, pressure, **humidity,** or temperature,		Y	Note: see GSPR 14.2b That should be treated in the risk assessment.
23.4 (s) 6th — precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user;		Y	Note: see GSPRs 10.4.1, 10.4.2, 10.4.4
23.4 (t) in the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, warnings and precautions, where appropriate, related to the general profile of interaction of the device and its products of metabolism with other devices, medicinal products and other substances as well as contra-indications, undesirable side-effects and risks relating to overdose;		NA needs justification	Note: see GSPR N° 12.2

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
23.4 (v) **warnings (1)** or precautions to be taken **in order to facilitate the safe disposal of the device, its accessories and the consumables used with it, if any. This information shall cover, where appropriate: – infection or microbial hazards such as explants, needles or surgical equipment contaminated with potentially infectious substances of human origin, and – physical hazards such as from sharps. If in accordance with the point (d) of Section 23.1 no instructions for use are required, this information shall be made available to the user upon request.**		Y	The Argon itself cannot be re-conditioned but the cylinder may be re-used so the user has to send it back empty for re-filling to the manufacturer. The empty cylinder shall be disposed of only by the owner in case it shall not pass the periodic retest required for T-PED/ADR.
23.4 (y) date of issue of the instructions for use or, if they have been revised, date of issue and identifier of the latest revision of the instructions for use;		Y	
23.4 (z) a notice to the user and/or patient that any serious incident that has occurred in relation to the device should be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.		Y	

Table 2 - not applicable requirements

Not applicable requirement numbers	Justification
9; 23.4(x)	The device is not referred to in Annex XVI.
10.1(c); 19.1 - 19.4; 23.2(s); 23.4(u, aa)	The device is not implantable.

14.6; 15.1; 15.2	The device has no measuring function.
22.1; 22.2; 23.4(w)	The device is not intended to be used by lay users.
16.1 - 16.4; 23.4(r)	The device does not emit or is a source of radiations.
11.1(c)11.4-11.8; 23.4(l, m); 11.3	The device is not sterile or intended to be sterilized or it does not have a specific microbial state.
23.2(n,o);23.4 (p)	The device is not for single use.
14.2(d); 17.1-17.4; 23.4(ab)	The device does not incorporate software.
23.2(q)	The device is not for clinical investigation only.
18.4 -18.8	The device is not active.
13.1-13.3; 23.4(4th-5th indents point s)	The device does not utilise tissues or cells, or their derivatives, of human origin or biological substances.
11.1(a,b)	The device cannot generate cuts and pricks.
23.2(p)	The device is not custom made.

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