TECHNICAL BULLETIN

Prepared by WG-15 TB 46/22 –December 2022

General Safety and Performance Requirements of Medical Device Regulation applied to Liquid Nitrogen

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 liquid nitrogen (LIN) as a medical device, i.e for cryotherapy and cryopreservation, and to provide recommendations on how to implement them.

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

Summary

This Technical Bulletin analyses all the requirements, it divides them between those certainly not applicable, those certainly applicable and includes justification when the applicability or not needs to be clarified.
Moreover, it 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. 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 14971:2019 (5.2-5.3)	Y	The intended purposes of LIN are cryotherapy, cryosurgery and cryopreservation for human cells and tissues. More detailed purposes shall be described by each manufacturer according to its Clinical evaluation. The patient population refers to the detailed purposes. Specific exclusions shall be described. The users of the LIN are healthcare professionals. The user of the dewars or cryogenic vessels (for transport, preparation...) may also be a technician. The performances required by the LIN: is linked for all the cases to the cryogenic temperatures. However conditions of the package may affect the availability of the product. The quality of LIN (the quality shall not be less than PhEUR one). The risk/benefit ratio shall be addressed by the risk management plan. The validation of the performances for LIN is done during the validation of the filling process where the quality of the gas is verified. Note: each manufacturer shall determine where to stop its responsibility on product compliance: - customers' dewars/vessels that are not pressurised can be contaminated, it may be responsibility of the manufacturer to determine which impurities can be from

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			the customer and which ones can be from the LIN itself.
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 14971:2019 (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 14971:2019.
3. Manufacturer shall establish, implement, document and maintain a risk management system.	ISO 14971:2019 (4)	Y	Each manufacturer shall have a risk management system in place following the ISO 14971:2019 (or GMP). The system shall be documented.
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 14971:2019 (4.1;4.2) ISO 13485:2016 (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 14971:2019 (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 14971:2019 (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 14971:2019(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 14971:2019 (7)	Y	The risk management plan defines the measures for risks reduction, such as controls during production.

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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 14971:2019 (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 14971:2019 (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.
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 14971:2019 (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 14971:2019 (7.1a)	Y	The risk management plan shall describe the 3 criteria. (design, alarms, IFU)
4. (b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated; and	ISO 14971:2019 (7.1b)	Y	The risk management plan shall describe the 3 criteria. (design, alarms, IFU)
4. (c) provide information for safety (warnings / precautions / contraindications) and, where appropriate, training to users.	ISO 14971:2019 (7.1c) EN ISO 15223-1	Y	The risk management plan shall describe the 3 criteria. (design, alarms, IFU)

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4. (continue) The manufacturer shall inform users of any residual risks.	ISO 14971:2019 (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 LIN are related to: - the safety of "handling the container"; - the use on the patient; - the sampling storage management; - the interface with the other device (e.g., cryotherapy machines and probes). Note: only the general information about checking 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 14971:2019 (5.2, 5.3, 5.4, 7)	Y	The containers and their closure systems used for transport or store the device (LIN) are designed by respective manufacturers applying the standards (norms/regulations) for their approval under PED/TPED directives. The LIN manufacturer when is responsible for the container and closure system verifies that it has been approved.
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 14971:2019 (5.2, 5.3, 5.4) IEC 62366-1:2015+A1:2020 (5.1; 5.2;5.3; 5.4; 5.6)	Y	The target users are: - healthcare professionals - the technician within the hospital or nurses for the preparation for use (i.e. connection with other devices), and after use. 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 14971:2019 (5.2, 5.3, 5.4)	Y	The lifetime of the gas is linked to the container evaporation rate. Maintenance is not required to the user unless they are the owners of the containers, in such cases maintenance is out of the manufacturer's responsibility. Manufacturer is responsible of owned transport or storage container.
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 LIN storage conditions are derived by the MSDS (temperature for example); Some of containers (vessels) are approved according to T-PED directive, some other under PED directive like tanks. 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 Safe Transport of Gases - Doc 23/18 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 14971:2019 (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**

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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 requirements answers.
10.1 (a) the choice of materials and **substances** used, particularly as regards toxicity and, where appropriate, flammability;	ECHA N_2 toxicological profile	Y	The toxicity profile of LIN 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	LIN is stored in Stainless steel containers: AISI 316 and 304 are the most common used ones, these two materials are listed as compatible with Nitrogen in ISO 11114-1 which is considered as reference for materials compatibility also for cryogenic vessels (excluding oxygen) by the ISO 21010 "Cryogenic vessels — Gas/material compatibility"; Moreover both these materials are also used in surgical tools as stated in ISO 7153-1:2017 Surgical instruments — Materials — Part 1: Metals" that lists the materials compatible with surgical tools). The bio-compatibility between the gas and the body shall be anyway described in the biocompatibility report part of the technical documentation. Note: according to indication of use the risk to be evaluated is not the same if there is contact with the patient (e.g. for cryotherapy) it shall be addressed.
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.

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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 LIN.
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	Containers are purchased T-PED and PED approved.
10.1 (g) surface properties; and		NA needs justification	The containers do not require specific internal surface treatments.
10.1 (h) the confirmation that the device meets any defined chemical and/or physical specifications		Y	The LIN shall conform to the Ph. Eur. specification as a minimum (or the specifications 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. Note: Risks are different and the manufacturer shall evaluate accordingly if the “not pressurized dewars” are filled.
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		Y	The device is a gas itself. Nevertheless the instruction for use shall inform about the need of compatibility with LIN of the other devices used in combination.

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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.			
10.4. Substances	Title	Title	Title
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	The risk of residues deriving from previous fillings of the container shall be considered in the risk management. Comments: no degradation possible - no debris released from the device.
10.4.1 Devices, or those parts thereof or those materials used therein that:		Y/N	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		Y	Vessels containing LIN are usually made of Stainless steel which compatibility with the body is acceptable since are also used in surgical tools as stated in ISO 7153-1:2017 " Surgical instrument materials TITLE. Valves used for transfer can be made of brass which contains Pb above 0.1% w/w. EIGA Doc 216 on elemental impurities in Medicinal gases evaluated the content of elemental impurities, inlcuding Pb, with a worst case scenario approach: the conclusions are that there is no risk for the patient. Since LIN when used in contact with the patient has a very short time of exposure and it is not absorbed, the EIGA Doc 216 conclusions can be extended also to LIN.

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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	LIN is not by itself a CMR or endocrine disruptor.
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 pursuant to Section 10.4.2:		Y	See answer to **10.4.1 1st indent.**
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 N2 toxicological profile	NA needs justification	LIN is not by itself a CMR or endocrine disruptor
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 health	ECHA N2 toxicological profile	NA needs justification	LIN is not by itself a CMR or endocrine disruptor.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
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.	ECHA N2 toxicological profile	NA needs justification	LIN is not on the list of mutagenic products

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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	No phthalates are present in LIN.
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.		NA needs justification	See answer to **10.4.1 1st indent.**

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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.		NA needs justification	See answer to **10.4.1 1st indent.**
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	Risks related to manufacturing, transport and storage shall include evaluation of residues and contaminates, to be identified in the risk assessment. Note: Risks are different and the manufacturer shall evaluate accordingly if the “not pressurized dewars” are filled.
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 GSPR 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	Not applicable for pressurized containers. If the manufacturer considers the filling of non-pressurized open dewar, it has to analyse this requirement in the Risk Assessment document.

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11.1 (c) reduce as far as possible any microbial leakage from the device and/or microbial exposure during use,			In cryopreservation there could be leakage from contaminated vials in liquid nitrogen and in cryotherapy the contamination could come from repeated dipping of the same swabs in the liquid nitrogen. This is to be considered in the Risk Assessment.
11.1 (d) prevent microbial contamination of the device or its content such as specimens or fluids			See GSPR 11.1.
11.2. Where necessary devices shall be designed to facilitate their safe cleaning, disinfection, and/or re-sterilisation.		NA needs justification	See GSPR 11.1. the safe cleaning can be carried out only on the dewar when refilling take place (in the filling station).
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	Non applicable because nitrogen it's not 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	Nitrogen is not intended to be introduced into the human body and it is non absorbed or locally dispersed. See justification in EIGA TB 30.
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 misconnection**.		Y	The delivery to fixed tanks is carried out through gas – specific connections that have been agreed at EIGA level (DOC 909 / 20 - EIGA Cryogenic Gases Couplings for Tanker Filling), the delivery is carried out drivers trained by EIGA members therefore the risk is limited. If the tank is connected to a pipeline then the risk of misconnection has been verified at the time of pipeline installation. A disclaimer shall be included in instruction for user to check that the right gas is connected to the downstream devices.

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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 pressurized vessels must be selected as appropriate for the gas and to withstand liquid nitrogen conditions and T-PED or PED approved.
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 LIN is temperature variations. These shall be addressed in the risk assessment.
14.2 (c) the risks associated with the use of the device when it comes into contact with materials, liquids, and substances, including gases, to which it is exposed during normal conditions of use;		Y	The compatibility with LIN shall be considered for devices used in combination with LIN, and the cooling effect has to be considered.
14.2 (e) the risks of accidental ingress of substances into the device		Y	For pressurized containers the management of hoses during transfilling have to be considered in the risk assessment. With regard to not pressurized dewars the requirement has to be considered in the Risk Assessment document.
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 LIN.

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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 applicable to the gas. The risks are related to the aging of the pressurized containers that are periodically re-tested according to PED/TPED.
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	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 containers needs to undergo to periodic tests according to the T-PED/PED/ADR requirements. These tests are responsibility of the container 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 GSPR 14.1.
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	Table C.2 ISO 14971:2019	Y	Disposal of the container shall be carried out by the container owner when the periodic inspection fails. Gas disposal is not applicable: the container has to be sent back to the gas manufacturer for refilling when empty or not used.

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for use.			
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	The single fault condition is “not reaching temperature” but temperature is a physical characteristic of the liquid nitrogen thus it is not possible. The other fault condition, but not as single fault, to be considered is that the container is not maintaining the vacuum isolation and higher evaporation occurs.
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 LIN.
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 14971:2019	NA needs justification	No external power supply is applicable LIN.
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 patient and user against mechanical risks connected with, for example, resistance to movement, instability and moving parts.		Y	The dewars must be protected from falls. The risk shall be evaluated in the risk assessment. Not applicable for tanks.
20.2. Devices shall be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from		NA needs justification	The Dewars and tanks do not create vibration when LIN is extracted for its use.

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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.			
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 valves used also for transfilling operations 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.		Y	The connections for the device are considered the valves used on the transport or storage containers. These are separately approved by respective manufacturers according to PED or T-PED directives as appropriate.
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.		Y	The only possible fitting/refitting is the of connection/disconnection of hoses or opening /closing lids. The correct connection/disconnection or opening /closing shall be addressed by instruction to operators (e.g. in case of fixed tank deliveries) or users (e. g. in case of not- pressurized dewars).
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		NA needs justification	Liquid nitrogen is used for its low temperature, therefore the risk of cold burns cannot be fully avoided, and can be minimised only by using appropriate PPE.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
conditions of use.			
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 14971:2019	NA needs justification	It refers to the devices used in combination with LIN 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 release of dangerous levels of energy **or substances** from an energy and/or substance source.	Table C.1 ISO 14971:2019	NA needs justification	It refers to the devices used in combination with LIN for its delivery to the patient.
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 14971:2019; :2020 IEC 62366-1:2015+A1:2020	NA needs justification	It refers to the devices used in combination with LIN 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**

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. 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 portable containers are provided with label and leaflet (i.e. Instruction for use). For fixed tanks or loose product (e.g. delivered with road tankers) the instruction for use are delivered to the customer with the first delivery since the fixed installation is far from the point of use (external to the building) or the container is not left to the customer. If the manufacturer has a website the instruction for use shall be made available and kept up to date on the website.
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	IEC 62366-1:2015 + A1:2020	Y	See GSPR 23.1 general. The usability should consider that the user can understand 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 can be placed only on the portable container. For fixed tanks or loose product (e.g. delivered with road tankers) the label is delivered to the customer with the first delivery since the fixed installation is far from the point of use (external to the building) or the container is not left to the customer. In such cases UDI can be reported on the delivery note (or other document delivered with the product).

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 (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	Usually there are instruction for use for the safe handling of the product. See GSPR to 23.1 general.
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.		Y	Since for fixed tanks or loose product (e.g., delivered with road tankers) the manufacturer is delivering multiple times the same device to a single user/location (See GSPR 23.1 general) a single copy of the Instruction for use may be delivered.
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 LIN containers 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.

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 (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 15223-1:2021	Y	The symbols used shall be derived from ISO 7000, ISO 7010, ISO 15223-1.
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	
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 cryopreservation, cryotherapy …)
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		NA Need justification	See GSPR 10.4.1: not applicable.

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 (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 15223-1:2021 (5.1.7)	Y	The LIN 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 15223-1:2021 (5.7.10)	Y	The UDI carrier may be identified with the symbol EN 15223 5.7.10 (UDI) UDI carrier can be reported on the delivery note (or other document delivered with the product) when the device is delivered in fixed tanks or loose product.
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 15223-1:2021 (5.12)	Y	The expiry date of the LIN has been defined in GSPR N. 6. The label shall report this expiry date, according to the production date of the batch. The date can be reported on the delivery note (or other document delivered with the product) when the device is delivered in fixed tanks or loose product. 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 serial number, provided the date is clearly identifiable;	EN ISO 15223-1:2021 (5.1.3)	NA needs justification	The previous GSPR is used.
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 containers, keep in a ventilated room…
23.2 (q) an indication that the device is a medical device.	EN ISO 15223-1:2021 (5.7.7)	Y	The ISO 15223 symbol 5.7.7 may be used.

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 (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.
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 LIN since it is class IIA.
23.4 (e) the performance characteristics of the device;		Y	It shall be conforming to what indicated in the technical documentation (part 1).

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 (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 that devices shall withstand liquid nitrogen temperatures, etc.
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 container for its use are deriving from risk assessment (e.g. how to connect the container, 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 nitrogen properties such as low temperatures and under oxygenation risks. The user of the gas shall be a trained healthcare professional for the application indicated as intended purpose.
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 container 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,		NA Justification needed	Maintenance activities are not possible on the device, nor cleaning or disinfection.

MDR, General Safety and Performance Requirements of Regulation, (EU) 2017/745	**applicable standards - general guide - specific points and subpoints (related MDR)**	applicable?	Response
– identification of any consumable components and how to replace them,		NA needs justification	No consumables components are foreseen for the container.
– 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 container 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)
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 container is empty. The container itself is reusable, however the empty container shall be re-filled by the manufacturer, and not by the user therefore information on its reuse is not applicable for the device.

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 (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 LIN.
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.
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	Warning that affects safety are related to under oxygenation and cold burns. Other may be related to malfunction of the container such as: of the valve in case of pressurised equipment or loosing of vacuum by the dewar.
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	External temperature affects the evaporation of LIN. Note: see GSPR 14.2b That should be treated in the risk assessment.

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) 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;		NA Needs justification	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
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 LIN itself cannot be re-conditioned but the container may be re-used, since there are different delivery options each manufacturer shall determine where to stop its responsibility on product compliance and if safe disposal need to be disclosed (e.g. The empty container shall be disposed off only by the owner in case it shall not pass the periodic retest required for T-PED/ADR).

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 (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.