TECHNICAL BULLETIN

Prepared by WG-15 TB 30/24 – May 2024

Classification of Medical Device Gases According to European Medical Device Regulations

Introduction

This Technical Bulletin has been prepared by specialists from EIGA Member Companies and is their interpretation and opinion of how medical gases meeting the definition of medical devices should be classified according to specific regulations or legislation. This Technical Bulletin is not a legally binding interpretation and for this reference needs to be made to the appropriate authority.

Carbon dioxide (CO_2), nitrogen, argon as well as other gases depending on their purpose in medical applications need to be defined as medical devices. A classification based on the risk is defining the required procedure for CE marking of the medical device, see [1] and [2].

With the introduction of 2017/745/EU also known as Medical Device Regulation, (MDR) [2] some uncertainties on classification due to the new classification rule 21 for substance-based medical devices occurred.

Scope

Classification of carbon dioxide, nitrogen and argon as medical devices according MDR classification rules. Further gases could be included in updates.

Purpose

This Technical Bulletin puts forward an EIGA position that provides guidance for the classification of medical device gases to establish a harmonised approach and to avoid different interpretations of rules and risk classes across the different EU member states.

Summary

Based on the information detailed in the sections below, the proposed classification for the different applications of nitrogen (N_2), carbon dioxide and argon according to the Medical Device Regulation (MDR) 2017/745/EU are the following:

Product	Intended Use	Classification MDR
Nitrogen (N_2) – Liquid	Cryopreservation, cryotherapy (including cryosurgery)	IIa
Nitrogen (N_2) – Gaseous	Source of supply for incubators	Not a MD
Carbon dioxide (CO_2) – Gaseous	Insufflation during minimal invasive surgery and colonoscopy	IIa
Carbon dioxide (CO_2) – Gaseous	Source of supply for incubators	Not a MD
Carbon dioxide (CO_2) – Liquid	Cryotherapy (including cryosurgery)	IIa
Pure gases (CO_2; N_2; O_2) or their Mixtures	In vitro buffer for Human cells culture, including IVF	I
Argon	Plasma coagulation	IIa

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Definitions

Definitions from Medical Device Regulation (MDR) 2017/745/EU

MDR
Transient *means normally intended for continuous use for less than 60 minutes.*
Short term *means normally intended for continuous use for between 60 minutes and 30 days.*
Long term *means normally intended for continuous use for more than 30 days*
Body orifice *means any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma.*
Invasive device *means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body*
Surgically invasive device *means:* *(a) an invasive device which penetrates inside the body through the surface of the body, including through mucous membranes of body orifices with the aid or in the context of a surgical operation; and* *(b) a device which produces penetration other than through a body orifice.*
Implantable device *means any device, including those that are partially or wholly absorbed, which is intended:* *- to be totally introduced into the human body, or* *- to replace an epithelial surface or the surface of the eye,* *by clinical intervention and which is intended to remain in place after the procedure.* *Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device*
Active medical device *'active device' means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices.* *Software shall also be deemed to be an active device*
Active therapeutic device *means any active device used, whether alone or in combination with other devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or disability.*
Active device intended for diagnosis and monitoring *means any active device used, whether alone or in combination with other devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.*
Injured skin or mucous membrane *means an area of skin or a mucous membrane presenting a pathological change or change following disease or a wound.*

Definitions from MDCG 2021-24

Systemic absorption*: The process by which substances or their metabolites enter the body (e.g. by crossing mucous membranes) and are distributed into the body via the blood and/or lymphatic system.*
Wholly or mainly absorbed*: The term 'absorption' in the context of implantable devices refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body. It does not apply to those substances that are excreted without modification from the body, e.g. insufflation gases for the abdominal cavity or laparoscopic and endoscopic procedures.*
Local dispersion*: The condition by which substances remain in a specific site without being distributed into the body via the blood and/or lymphatic system.*

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Other definitions

Cryotherapy: A generic term that is used to describe therapies which are based on the use of low temperatures and includes cryosurgery as specific application.

Conventions

The portions of text of the classification rules that apply to the medical device gas under examination are underlined.

The rules or parts of rules which are not applicable but need an explanation or a rationale for that are shown.

The rules or parts of rules whose non-applicability is obvious are not shown.

Nitrogen (N_2)

Liquid nitrogen for cryopreservation of human samples for medical purpose

When liquid nitrogen is used for preservation of cells and tissues of human origin, intended to be re-implanted or re-used in the human body, it shall be considered as a medical device, even if direct contact with biological material does not occur. See [5] for further information.

MDR
Rule 2 *All non-invasive devices intended for channelling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa:* *– if they may be connected to a class IIa, class IIb or class III active device; or* *– if they are intended for use for channelling or storing blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags; blood bags are classified as class IIb.* *In all other cases, such devices are classified as class I.*
Conclusion: IIa

Liquid nitrogen for cryotherapy
LIN used as a source of cold for a cryoprobe. There is no contact of LIN with the tissue .

MDR
Rule 9 *All active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are classified as class IIb.*
Comments The "*potentially hazardous way*" is not retained because the application is made through a device that control the energy. Liquid nitrogen is only the source of cold
Conclusion: IIa

Liquid nitrogen for topical cryotherapy
In this use, LIN is applied directly on the tissue, for example in dermatology.

MDR
Rule 4 *All non-invasive devices which come into contact with injured skin or mucous membrane are classified as:* [..]

class IIa in all other cases.
Rule 9 *All active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are classified as class IIb.*
Comments The "*potentially hazardous way*" is not retained because the application is made through a device that control the energy. Liquid nitrogen is only the source of cold.
Conclusion: IIa

Carbon dioxide

Gaseous carbon dioxide for insuflation during minimal invasive surgery
Carbon dioxide is surgically introduced for inflating body cavities to increase working and viewing space during minimal invasive surgery. Since such a procedure can have a duration of a few hours, its *short-term use* means Rule 6 and Rule 8 do not apply.

MDR
Rule 7 *All surgically invasive devices intended for short-term use are classified as class IIa unless they:* *[..]* *— have a biological effect or are wholly or mainly absorbed in which case they are classified as class III;* [..]
Comments
"*to be wholly or mainly absorbed*" is not applicable because MDCG 2021-24 definition says that "It does not apply to those substances that are excreted without modification from the body, e.g. insufflation gases for the abdominal cavity or laparoscopic and endoscopic procedures."
The MDCG document 2021-24 in the examples referred to the first paragraph of this rule includes the "gases for insufflation" which is applicable to CO2 used in laparoscopy.
Conclusion: IIa

Gaseous carbon dioxide for insuflation during colonoscopy
Colonoscopy is a procedure where carbon dioxide is introduced via the rectum (body orifice) to distend the gastrointestinal lumen for safe advancement of endoscopes (gastrointestinal endoscopy) and for visualization with imaging systems (virtual colonoscopy).

Carbon dioxide for colonoscopy is:

- an invasive device with respect to natural body orifice (introduction via the rectum);
- foreseen for short term use;
- a device that is composed of substances (one unique substance: CO_2); and
- intended to be introduced into the human body via a body orifice (rectum).

Carbon dioxide for colonoscopy is not:

- a surgically invasive device;
- wholly or mainly absorbed in the human body because most of the gas is removed via the natural body orifice and just residuals are absorbed and finally excreted without modification from the body;
- intended for connection to an active medical device; and
- an active medical device.

NOTE CO_2 is introduced under a certain pressure in the body by the administration device. It is that device that regulates the pressure in the body. The fact that CO_2 is stored in pressurised cylinders is irrelevant.

Therefore, classification rules 5 and 21 have to be considered. Rule 9 does not apply.

MDR
Rule 5: *All invasive devices with respect to body orifices, other than surgically invasive devices, which are not intended for connection to an active device or which are intended for connection to a class I active device are classified as:* *— class I if they are intended for transient use;* *— class IIa if they are intended for short-term use, except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in the nasal cavity, in which case they are classified as class I; and* *All invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to a class IIa, class IIb or class III active device, are classified as class IIa.*
Comments CO_2 as a substance is not (physically) connected to an active medical device (as the examples referred to in [4] for this specific rule). CO_2 for this application is seen to be an operating supply. The MDCG document 20212-24 in the examples referred to the second indent of this rule includes the “gases for insufflation” which is applicable to CO2 used in colonoscopy.
Rule 21: *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 are classified as:* *— class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;* *— class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;* *— class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and* *— class IIb in all other cases.*
Comments “absorption” and “systemic absorption” is not applicable because MDCG 2021-24 definition says that “It does not apply to those substances that are excreted without modification from the body, e.g. insufflation gases for the abdominal cavity or laparoscopic and endoscopic procedures.” Local dispersion is not applicable since the CO2 does not remain in the body. As a consequence, this rule is not applicable.
Conclusion: IIa

Carbon dioxide for cryotherapy
Carbon dioxide used as a source of cold for a cryoprobe. There is no contact of carbon dioxide with the tissue.

MDR
Rule 9 *All active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are classified as class IIb.*
Comments The “*potentially hazardous way*” is not retained because the application is made through a device that control the energy. Liquid carbon dioxide is only the source of cold.
Conclusion: IIa

Carbon dioxide for topical cryotherapy
In this use, liquid phase carbon dioxide is used to apply directly on the tissue, for example, dermatology.

MDR

Rule 4 *All non-invasive devices which come into contact with injured skin or mucous membrane are classified as:* [..] *Class IIa in all other cases.*
Rule 9 *All active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are classified as class IIb.*
Comments The "*potentially hazardous way*" is not retained because the application is made through a device that control the energy. Liquid carbon dioxide is only the source of cold.
Conclusion: IIa

Pure gases (CO2; N2; O2) or their Mixtures as in vitro buffer for Human cells culture, including IVF

CO2, O2 and N2 are often connected to the human cells' incubator separately and the incubator itself carries out a pre-set programme for their mixture. However, these gases could also be provided pre-mixed in cylinders. Their mode of action is to maintain the pH of the buffer solution, via a gas exchange on the surface of the culture media.

Note: If the incubator is used for other applications such as research purposes or diagnostic purposes (bacteria growth) the gases are considered as general laboratory use.
Note: If the bacteria to be grown are part of the microbiota to be implanted in the human body, anyway the definitions hereafter do not apply being bacteria not human tissues or cells, blood, other body liquids or other liquids.

MDR
Rule 1 *All non-invasive devices are classified as class I, unless one of the rules set out herein after applies.*
Comments Being the substance or mixture of substances indicated for a medical application (human cells culture), but being not even in direct contact with the cells, they are not invasive medical devices, This is the only applicable rule for not invasive device.
Rule 2 *All non-invasive devices intended for channelling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa: — if they may be connected to a class IIa, class IIb or class III active device; or — if they are intended for use for channelling or storing blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags; blood bags are classified as class IIb. In all other cases, such devices are classified as class I.*
Comments The gases whose function is to maintain the pH of the buffer solution are not containers for storage, nor are they used for transport; therefore Rule 2 is not applicable.
Rule 3 *All non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids intended for implantation or administration into the body are classified as class IIb, unless the treatment for which the device is used consists of filtration, centrifugation or exchanges of gas, heat, in which case they are classified as class IIa.* *All non-invasive devices consisting of a substance, or a mixture of substances intended to be used in vitro in direct contact with human cells, tissues or organs taken from the human body or used in vitro with human embryos before their implantation or administration into the body are classified as class III.*
Comments The gases are not intended to modify the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids but to maintain the pH of the media solution. The gases whose function is to maintain the pH of the media solution and therefore to provide a favourable environment for the culture of embryos do not achieve their intended purpose in direct contact with the

embryo.
Conclusion: I

Argon

Argon for plasma coagulation
Plasma coagulation is a procedure where Argon is surgically used in the body for the coagulation of tissues by Argon ionisation (Argon plasma) through the application of an electrical current generated by the electrosurgical coagulator.

Rule 6 *All surgically invasive devices intended for transient use are classified as class IIa unless they:* *[..]* *— have a biological effect or are wholly or mainly absorbed in which case they are classified as class IIb;* [..]
Comments
"*to be wholly or mainly absorbed*" is not applicable because MDCG 2021-24 definition says that "It does not apply to those substances that are excreted without modification from the body" however Argon has a *"biological effect"* is not applicable since it does not actively and intentionally induce, alter or prevent a response from the tissues that is mediated by specific reactions at a molecular level.
Rule 9 *All active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way…*
Comments
The rule is not applicable because the exchange of energy with the body is not carried out by argon itself but by the plasma produced and regulated by electrosurgical coagulator, of which Argon is an accessory. Note: the argon coagulation unit itself is instead is class IIB as potentially hazardous, according to the manual of borderline and classification (version 3) since is the unit that "directly influence the argon plasma coagulation".
Conclusion: IIa

Conclusions

For liquid nitrogen intended for cryopreservation and cryotherapy, the conclusion on classification according to 2017/745/EU (MDR) is class IIa.

For carbon dioxide (CO_2) intended for insuflation (e.g. laparoscopy, colonoscopy), the conclusion on classification according to 2017/745/EU (MDR) is class IIa.

For carbon dioxide intended for cryotherapy, the conclusion on classification according to 2017/745/EU (MDR) is class IIa.

For gases (CO2; N2; O2) or their Mixtures as in vitro buffer for Human cells culture, including IVF, the conclusion on classification according to 2017/745/EU (MDR) is class I.

For Argon intended for plasma coagulation the conclusion on classification according to 2017/745/EU (MDR) is class IIa.

EIGA interpretation of MDA, MDT, MDN codes for medical device gases

The Commission Implementing Regulation (EU) 2017/2185 [12] sets out the list of MDA, MDT, MDN codes and corresponding types of devices for the purpose of specifying the scope of the designation as notified bodies in the field of medical devices under Regulation (EU) 2017/745 [2].

The following table shows the possible applicable codes to medical device gases, based on the interpretation of EIGA members.

CODE	DESCRIPTION	CO_2 for cryotherapy	CO_2 for insufflation	Liquid N_2 for cryotherapy and cryopreservation	Argon for plasma coagulation
MDA 0303	Active non-implantable devices utilising hyperthermia / hypothermia	X		X	
MDA 0314	Active non-implantable devices for processing and preservation of human cells, tissues or organs including in vitro fertilisation (IVF) and assisted reproductive technologies (ART)			X	
MDN 1213	Non-active non-implantable devices composed of substances to be introduced into the human body via a body orifice or the dermal route		X		
MDN 1214	General non-active non-implantable devices used in health care and other non-active non-implantable devices				X
MDT 2011	Devices which require packaging, including labelling	X	X	X	X

References

[1] 93/42/EEC – *Medical Device Directive* www.europa.eu

[2] 2017/745/EU – *Medical Device Regulation* www.europa.eu

[3] GHTF/SG1/N77:2012 -- *Principles of Medical Devices Classification* www.imdrf.org

[4] MEDDEV 2.4/1 rev. 9, www.ec.europa.eu

[5] *Manual on borderline and classification in the community regulatory framework for medical devices; version 1.18* www.ec.europa.eu

[6] NORCCAP *(Norwegian colorectal cancer prevention): a randomised trial to assess the safety and efficacy of carbon dioxide versus air insufflation in colonoscopy*. Gut 2002 Bretthauer M, Thiis-Evensen E, Huppertz-Hauss G, Gissels - son L, Grotmol T, Skovlund E, Hoff G. www.ncbi.nlm.nih.gov

[7] *Meta-analysis: the use of carbon dioxide insufflation vs. room air insufflation for gastrointestinal endoscopy. Aliment Pharmacol Ther, 2012* Wang WL, Wu ZH, Sun Q, et al www.ncbi.nlm.nih.gov

[8] *The use of carbon dioxide for insufflation during GI endoscopy: a systematic review. Gastrointest Endosc, 2009* Dellon ES, Hawk JS, Grimm IS, Shaheen NJ. www.ncbi.nlm.nih.gov

[9] *Carbon dioxide insufflation during colonoscopy in deeply sedated patients, World Journal of Gastroenterology ,2012 Singh* et. al.www.ncbi.nlm.nih.gov

[10] *Training in diagnostic laparoscopy (Archived) from the original on July 14, 2014. Retrieved October 10, 2013* www.gfmer.ch

[11] *Volume and Composition of Human Intestinal Gas Determined by Means of an Intestinal Washout Technique, The New England Journal of Medicine, 1971* Michael D. Levitt www.nejm.org

[12] Commission Implementing Regulation (EU) 2017/2185 on the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation as notified bodies in the field of medical devices under Regulation (EU) 2017/745

NOTE The medical publications in [5,6,7,8,9, and 10] are given as examples. Further information can be found in manufacturers' clinical evaluation reports.

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