TECHNICAL BULLETIN

Prepared by WG-15 TB 30/19 – May 2019

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) and liquid nitrogen (LIN) 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 and liquid nitrogen as medical devices according MDD and 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) and carbon dioxide according the Medical Device Directive (MDD) 93/42/EEC and the Medical Device Regulation (MDR) 2017/745/EU are the following:

Product	Application	Classification MDD	Classification MDR
Nitrogen (N_2) – Liquid	cryopreservation, cryosurgery and cryotherapy	IIa	IIa
Carbon dioxide (CO_2) – Gaseous	laparoscopy	IIa	IIa
Carbon dioxide (CO_2) – Gaseous	colonoscopy	IIa	IIb
Carbon dioxide (CO_2) – Liquid	cryotherapy	IIa	IIa

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Definitions

Definitions from Medical Device Directive (MDD) 93/42/EEC and from Medical Device Regulation (MDR) 2017/745/EU

MDD	MDR
Transient *Normally intended for continuous use for less than 60 minutes.*	***Transient** means normally intended for continuous use for less than 60 minutes.*
Short term *Normally intended for continuous use for not more than 30 days.*	***Short term** means normally intended for continuous use for between 60 minutes and 30 days.*
Long term *Normally intended for continuous use for more than 30 days.*	***Long term** means normally intended for continuous use for more than 30 days*
Body orifice *Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma.*	***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 *A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.*	***Invasive device*** *'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 *An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.* *For the purposes of this Directive devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, shall be treated as surgically invasive devices.*	***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 *Any device which is intended:* *- to be totally introduced into the human body or,* *- to replace an epithelial surface or the surface of the eye,* *by surgical intervention which is intended to remain in place after the procedure.* *Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.*	***Implantable device*** *'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 *Any medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy.* *Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices.*	***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 therapeutical device	***Active therapeutic device** means any active device*

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MDD	MDR
Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap.	*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 for diagnosis *Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities*	***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.*
No specific definition in MDD	***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 MEDDEV 2.4/1 Rev. 9 – Classification of Medical Devices - Guidelines relating to the application of the council directive 93/42/EEC on medical devices

Remark: MEDDEV guidelines are, at the moment only applicable for directive 93/42/EEC, but due to the lack of definitions for regulation 2017/745/EU, these are considered to be further applicable.

Biological effect *All materials and devices have the potential to affect tissues following use in a surgically invasive procedure. A material is considered to have a biological effect if it actively and intentionally induces, alters or prevents a response from the tissues that is mediated by specific reactions at a molecular level. Such a device may be described as bioactive.* [From *Explanations of special concepts*, Note 5 of section Rule 6]
Absorption*: The term absorption refers to the degradation of a material within the body and the metabolic elimination of the resulting degradation products from the body.* [From *Explanations of special concepts* Note 6 of section Rule 6]

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.

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MDD	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 in class IIa:* *– if they may be connected to an active medical device in class IIa or a higher class,* *– if they are intended for use for storing or channelling blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags, which are in class IIb.* *In all other cases they are in class I.*	**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	**Conclusion: IIa**

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

MDD	MDR
Rule 9 *All active therapeutic devices intended to administer or exchange energy are in Class IIa unless their characteristics are such that they may administer or exchange energy to or from 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 in Class IIb.*	**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.	**Comments** Idem MDD
Conclusion: IIa	**Conclusion: IIa**

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

MDD	MDR
Rule 4 *All non-invasive devices which come into contact with injured skin:* [..] *— are in class IIa in all other cases, including devices principally intended to manage the micro-environment of a wound.*	**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 in Class IIa unless their characteristics are such that they may administer or exchange energy to or from the human body in a*	**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*

potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are in Class IIb.	*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.	**Comments** Idem MDD
Conclusion: IIa	**Conclusion: IIa**

Carbon dioxide

Gaseous carbon dioxide for laparoscopy
Laparoscopy is a procedure where carbon dioxide is surgically introduced for inflating body cavities to increase working and viewing space. Since such a procedure can have a duration of a few hours, the *short-term use* is retained and therefore rule 6 and rule 8 do not apply.

MDD	MDR
Rule 7 *All surgically invasive devices intended for short-term use are in Class IIa unless they are intended:* *[..]* *— or to have a biological effect or to be wholly or mainly absorbed in which case they are in Class III, [..]*	**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 The "*biological effect*" is not applicable because, in the meaning of the definition of MEDDEV 2.4/1 rev. 9, CO_2 does not "*intentionally induces, alters or prevents a response from the tissues*".	**Comments** The "*biological effect*" is not applicable because, in the meaning of the definition of MEDDEV 2.4/1 rev. 9, CO_2 does not "*intentionally induces, alters or prevents a response from the tissues*".
"*to be wholly or mainly absorbed*" is not applicable for two reasons: 1) most of the gas used during the insufflation procedure is removed from the body at the end of the procedure manually through the surgical openings (refer to [10]). 2) the small amount of CO_2 absorbed during the surgical procedure is excreted without any degradation through the respiratory process as CO_2 and, in accordance with GHTF document on classification of medical devices [3] page 15:, *"(b) This part of the rule* [wholly or mainly absorbed] *does not apply to those substances that are excreted without modification from the body.* *Example: Insufflation gases for the abdominal cavity."*	"*to be wholly or mainly absorbed*" is not applicable for two reasons: 1) most of the gas used during the insufflation procedure is removed from the body at the end of the procedure manually through the surgical openings (refer to [10]). 2) the small amount of CO_2 absorbed during the surgical procedure is excreted without any degradation through the respiratory process as CO_2 and, in accordance with GHTF document on classification of medical devices [3] page 15:, *"(b) This part of the rule* [wholly or mainly absorbed] *does not apply to those substances that are excreted without modification from the body.* *Example: Insufflation gases for the abdominal cavity."*
Conclusion: IIa	**Conclusion: IIa**

Gaseous carbon dioxide for 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.

MDD	MDR
Rule 5 *All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device or which are intended for connection to an active medical device in Class I: ◄* *— are in Class I if they are intended for transient use,* *— are in 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 a nasal cavity, in which case they are in Class I,*	**Rule 5**: *All invasive devices with respect to body orifices, other than surgically invasive devices, w*hich 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.
Conclusion: IIa	**Conclusion: IIa**

MDD	MDR
	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*

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	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 The principle given in GTHF document [10] regarding the fact that the absorption is not a criteria for being classified as class III when the device is absorbed but excreted without modification as used for CO_2 for laparoscopy, which states: "*[wholly or mainly absorbed] does not apply to those substances that are excreted without modification from the body.* *Example: Insufflation gases for the abdominal cavity.*" applies in the same way for colonoscopy, even if used in the gastrointestinal tract. **As a consequence, only the last part of the rule (other cases, IIb) needs to be considered.** It is also noted that: • CO_2 is naturally present in the lower gastrointestinal tract since it represents more than 10% of the intestinal gas in humans (refer to [11] or other public available sources). • CO_2, which is naturally present in the gastrointestinal tract, is not different from the CO_2 introduced during the colonoscopy.
	Conclusion: IIb

Liquid carbon dioxide for cryosurgery or cryotherapy
Liquid carbon dioxide used as a source of cold for a cryoprobe. There is no contact of carbon dioxide with the skin.

MDD	MDR
Rule 9 *All active therapeutic devices intended to administer or exchange energy are in Class IIa unless their characteristics are such that they may administer or exchange energy to or from 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 in Class IIb.*	**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.	**Comments** Idem MDD
Conclusion: IIa	**Conclusion: IIa**

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Liquid carbon dioxide for topical cryotherapy
In this use, liquid carbon dioxide is applied directly on the skin, for example, dermatology.

MDD	MDR
Rule 4 *All non-invasive devices which come into contact with injured skin:* [..] *— are in Class IIa in all other cases, including devices principally intended to manage the micro-environment of a wound.*	**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 in Class IIa unless their characteristics are such that they may administer or exchange energy to or from 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 in Class IIb.*	**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.	**Comments** Idem MDD
Conclusion: IIa	**Conclusion: IIa**

Conclusion

Based on the intended uses for nitrogen, the conclusion on classification on 93/42/EEC (MDD) and 2017/745/EU (MDR) is class IIa. The same classification rules are applicable.

For carbon dioxide intended for laparoscopy, the conclusion on classification on 93/42/EEC (MDD) and 2017/745/EU (MDR) is class IIa.

For carbon dioxide (CO_2) intended for colonoscopy, the conclusion on classification on 93/42/EEC (MDD) is IIa while on 2017/745/EU (MDR) is class IIb due to introduction of rule 21.

For carbon dioxide intended for cryotherapy, the conclusion on classification on 93/42/EEC (MDD) and 2017/745/EU (MDR) is class IIa.

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

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[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

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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