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Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices

April 2022

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.

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Contents

1. BORDERLINE PRODUCTS: MEDICAL DEVICES / MEDICINAL PRODUCTS

1.1 Introduction

The demarcation between the Regulation (EU) 2017/745 on medical devices (MDR) on the one hand and the Directive 2001/83/EC on the Community code relating to medicinal products for human use (MPD) on the other hand is crucial for the proper implementation of these sets of legislation and their correct interpretation and enforcement. Several provisions to establish the demarcation between the two legal frameworks have been laid down in the MDR and MPD. This document provides further explanations and examples clarifying these provisions in order to support the uniform application of the MDR across the EU. It has been elaborated by a working group including experts from Member States' competent authorities, the Commission services, European Medicines Agency[1] as well as a wide range of stakeholders, and has been endorsed by the Medical Device Coordination Group (MDCG) – the governance group of medical device competent authorities at EU level.

The document starts with the general discussion of the borderline between medical devices and medicinal products, including relevant definitions and examples. Separate chapters are dedicated to herbal products, substance-based devices and medical device and medicinal product combinations.

This guidance document may be revised to reflect up-to-date scientific and technical knowledge as well as the outcomes of the regulatory discussions within the MDCG Working Group on Borderline and Classification.

1.2 General principles and definitions

Borderline products are those where it is not clear from the outset whether they fall under the MDR or the MPD.[2]

In order to fall under the MDR a product must fulfil the definition of a medical device (Article 2(1) MDR) and must also not be excluded from its scope (Article 1(6) MDR). It is therefore necessary to examine both sets of prerequisites.

As a general rule, a product is regulated either by the MDR or by the MPD but not both. The conformity assessment procedure or the marketing authorisation procedure to be followed prior to placing a given product on the market will therefore be governed either by the MDR or by the MPD. The procedures of both regulatory regimes do not apply cumulatively. However, for products that have properties of both medicinal products and medical devices (*e.g.* medical devices incorporating as an integral part, a substance which, if used separately, would be considered to be a medicinal product), some cross-references are made within one regime to specific provisions of the other regime. For further details see Section 2.1.

[1] With the involvement of its scientific Committees.

[2] A separate guidance document is available covering borderline aspects of *in vitro* diagnostic medical device under Directive 98/79/EC: https://ec.europa.eu/docsroom/documents/10322/attachments/1/translations. It may be updated for Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices which replaces the Directive as of 26 May 2022. Please check the Commission medical devices page for up-to-date information and guidance: https://ec.europa.eu/health/md_sector/new_regulations/guidance_en

The definitions of medical device and medicinal product are reproduced here for reference:

1.2.1 Definition of medical device and medicinal product

1.2.1.1 Definition of medical device (Article 2 (1) MDR)

'medical device' *means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*

— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,

— providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

— devices for the control or support of conception;

— products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

For further considerations see Section 1.2.2 for definitions of pharmacological, immunological and metabolic means of action, and Section 1.2.3 for diagnosis.

1.2.1.2 Definition of an accessory of a medical device (Article 2 (2) MDR)

'accessory for a medical device' *means an article which, whilst not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s).*

1.2.1.3 Definition of medicinal product (Article 1(2) MPD)

medicinal product: (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

This definition comprises two limbs, one relating to presentation and the other to function. A product constitutes a medicinal product if it is covered by one or the other or both of those limbs.[3]

The first limb of this definition indicates that any substance presented as having properties for treating or preventing disease in human beings may be a medicinal product. In accordance with the first indent of Article 2(1) of the MDR, medical devices may also be intended to treat and prevent disease, along with other specific medical purposes. Therefore the decisive criterion for the demarcation between the two categories is the second limb of the medicinal product definition, which concerns the 'principal mode of action' of the product, see Section 1.2.2.

Due to the definition of medicinal product, substances used in or administered to human beings to make a medical diagnosis, even if they fulfil their function not by pharmacological, immunological or metabolic means as described in Section 1.2.2, are considered to be medicinal products.

The definition of medicinal product should be applied case-by-case and should be read in accordance with the case law of the European Court of Justice[4].

Article 2(2) of MPD provides that *"in cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply"*.

The wording of Article 2(2) of the MPD shows that it only applies if, after a case-by-case assessment, taking in consideration all the characteristics of a product, the product in question may fall within the definition of both, medical device and medicinal product. In such a case, the provisions of the MPD applies[5]. The MDR and the MPD may not be applied cumulatively.

1.2.2 Definitions of pharmacological, immunological, metabolic means

General aspects

According to Article 1(6)(b) of the MDR, in deciding whether a product falls under the MDR or the MPD particular account shall be taken of the principal mode of action of the product. The nature of the principal mode of action i.e. whether it is pharmacological, immunological or metabolic or other is generally the same irrespective of the quantity. See also Sections 1.2.5 and 4.1.

According to Article 2(1) MDR a medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but may be assisted in its function by such means. The concept that a medical device may be assisted in achieving its principal intended action by pharmacological, immunological or metabolic means should be understood as covering those cases when the medical device incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal

[3] Cf., for the former Directive 65/65/EEC: ECJ, C- 290/90 of 20.5.1992 "Eye lotions", ECR 1992 I-3317, para. 9
[4] Curia web page: http://curia.europa.eu/juris/recherche.jsf?language=en
[5] C-109/12 CJEU

product, and that has an action ancillary to that of the device. For further considerations see Sections 1.2.5 and 1.2.1.3.

Typically, the medical device's principal intended action is achieved by physical means (including mechanical action, physical barrier such as a film, lubrication, heat transfer, radiation, ultrasound, replacement of or support to organs or body functions). Furthermore, hydration or dehydration and pH modification may also be means by which a medical device achieves its principal intended action. See examples in the respective sections of the document, under 1.2.6.1 and 1.2.6.2.

For the purpose of this guidance document, the following three concepts may be distinguished.

1. '**Specific medical purpose'** (referred to in Article 2(1) MDR, first paragraph)

The specific medical purpose is specified by the manufacturer from those listed in the indents of Article 2(1) MDR.

2. '**Principal intended action**' (referred to in Article 2(1) MDR, second paragraph)

The principal intended action of a medical device is described in manufacturer's labelling and claims and must be based on state of the art scientific data regarding the principal mode of action, on a case-by-case basis.

3. '**Principal mode of action**' (referred to in Article 1(6)(b) MDR)

The principal mode of action represents the means by which the product achieves its principal intended action, i.e. pharmacological, immunological, metabolic, physical or other. It is objective and must be based on state of the art scientific data.

Although the manufacturer's claims are important, it is not possible to place the product in one or other regulatory category in contradiction with current scientific data. Manufacturers will be required to justify scientifically in the technical file their rationale for the qualification of their product. A product cannot be qualified as a medical device within the meaning of Article 2(1) of the MDR if it cannot be determined that the product's principal intended action is achieved by other than pharmacological, immunological or metabolic means. References to or making available by the manufacturer of information or data on safety or performance of the product is not relevant for the determination of its regulatory status.

Annex II to the MDR, point 1.1 *Device description and specification* requires under paragraph (e) that the manufacturer provides in the technical documentation the rationale for the qualification of the product as a device.

Annex VII to the MDR, point 4.2 *Notified body quotations and pre-application activities* requires under paragraph (d) that in respect to the pre-application activities the notified body has documented procedures requiring the review of pre-application information, including the preliminary verification that the product is covered by the MDR and its classification, prior to issuing any quotation to the manufacturer relating to a specific conformity assessment.

Annex VII to the MDR point 4.3 *Application review and contract* of the MDR requires under paragraph (b) that in respect to the formal application of the manufacturer, the notified

body has documented procedures to review application addressing amongst others the verification of the qualification of products covered by those applications as devices and their respective classifications.

Definitions of pharmacological, immunological and metabolic means[6]

The following definitions for pharmacological, immunological or metabolic means are intended to provide guidance as to the meaning of these terms in the context of determining the principal mode of action of the product.

'**Pharmacological means**' is understood as an interaction typically at a molecular level between a substance or its metabolites and a constituent of the human body which results in initiation, enhancement, reduction or blockade of physiological functions or pathological processes. Examples of constituents of the human body may include, among others: cells and their constituents (cell membranes, intracellular structures, RNA, DNA, proteins, e.g. membrane proteins, enzymes), components of extracellular matrix, components of blood and components of body fluids.

Examples of action via pharmacological means:

- interaction between a ligand (e.g. agonist, antagonist) and a receptor;
- interaction between a substance and membrane lipids;
- interaction between a substance and components of the cytoskeleton.

'**Immunological means**' is understood as an action initiated by a substance or its metabolites on the human body and mediated or exerted (i.e. stimulation, modulation, blocking, replacement) by cells or molecules involved in the functioning of the immune system (e.g. lymphocytes, toll-like receptors, complement factors, cytokines, antibodies).

Examples of action via 'immunological means':

- modulation of an immune response (e.g. suppressing, blocking, activating, enhancing);
- replacement, reconstitution or introduction of natural or modified immune cells or molecules;
- triggering an immune response against the targeted tissues, cells or antigens by immune-specific recognition;
- targeting action of other linked or coupled substances.

Examples of substances acting via immunological means: vaccine, tetanus anti-serum, monoclonal antibodies, CAR-T cells, anti-venom, C1 esterase inhibitor.

When immunological recognition is used to target or direct the effects of linked or coupled substances, this recognition cannot be considered an ancillary action. Such products would therefore be deemed to act via immunological means and cannot be considered a medical device.

[6] These definitions aim at adding more precision to the respective definitions present in MEDDEV 2.1/3 rev 3.

'**Metabolic means**' is understood as an action of a substance or its metabolites which involves an alteration, including stopping, starting or changing the rate, extent or nature of a biochemical process, whether physiological or pathological, participating in, and available for, function of the human body.

The term 'biochemical processes' is understood as reactions available for the human body including anabolic and catabolic reactions and transport of substances between compartments. An interaction with a known receptor is not a prerequisite for the metabolic means of action.

Examples of action via 'metabolic means':

- the movement of water due to active transport of electrolytes mediated by e.g. Na/K ATPase pumps;
- inhibition of endogenous enzymes, including the digestive enzymes;
- altering the electrolyte balance of the serum.

The definitions above should be read in conjunction with the following notes.

Note 1: In the context of these modes of action, a definition of the term 'substance' is given in Directive 2001/83/EC:

"***Substance**: Any matter irrespective of origin which may be:*
— human, e.g. human blood and human blood products;
— animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;
— vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts;
— chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis."

This definition of substance includes cells or molecules involved in functioning in the immune system.

The fact that a substance fits into the definition of the term 'substance' according to Article 1 (3) of Directive 2001/83/EC does not necessarily mean that the product may not be qualified as a medical device. Some types of substance are explicitly excluded from the scope of the MDR as per Article 1(6), for example viable biological material or viable organisms used in order to achieve or support the specific medical purpose of the product.

Note 2: Examples of 'interactions' include the following: covalent bonding, H-bonds, electrostatic, and van der Waals forces.

Note 3: For the determination of the principal mode of action of a product, only those effects that fall within the principal intended action (described in the manufacturer's labelling and claims and based on state of the art scientific data) of the product should be taken into account. See definition of 'principal mode of action' above.

Note 4: The 'action on the human body' is to be understood to include action on any of its constituents. Such constituents include also exogenous substances, organisms or pathogens within or on the body. For the purposes of applying the MDR, the definitions for

pharmacological, immunological, metabolic means of action also apply to explanted constituent parts of the body that are intended to be (re)introduced in the body or to assisted reproduction procedures.

Note 5: Although not an exhaustive criterion, the presence of a dose-response correlation is indicative of a pharmacological, metabolic or immunological mode of action.

1.2.3 Definition of medical diagnosis

For the purpose of this guidance document, this section is intended to clarify the borderline between medical devices and medicinal products used for diagnostic purposes.

'Diagnosis' is the process of investigation of the anatomy, morphology, the condition or the functions of the human body irrespective if these are physiological or pathological, and subsequent interpretation of this information with a view to determining possible abnormalities. In this context investigation can include visualisation, detection or measurement.

Note 1: Reference is made to the term 'diagnosis' as used in the definition of a medical device in Article 2(1) of MDR and to the term 'medical diagnosis' as used in the definition of a medicinal product according to Article 1 MPD. It should be understood that the terms 'diagnosis' and 'medical diagnosis' have the same meaning.

Note 2: As per the definition of a medicinal product in Article 1 (2)(b) MPD, the mode of action for the diagnostic substance(s) used in or administered to human beings is not a criterion for deciding the regulatory route, hence substances such as X-ray contrast media, NMR enhancing agents, SPECT- and PET-radiopharmaceuticals, fluorescein strips for diagnostic purposes, radioactive tracers, and substances for tumour identification are medicinal products.

Note 3: If the intended purpose of the product is to distinguish between healthy and pathological tissue *in vivo* or *ex vivo*, this would be regarded as diagnosis. However, if the intention is to simply visualise an anatomical structure without the aim to determine possible abnormalities, this would not be considered as diagnosis. For example, if the product is intended by its manufacturer to be used to stain or mark an anatomic area in order to help a procedure or to adequately position or adjust a medical device, the product could be qualified as a medical device or as an accessory to a medical device. Therefore products should be considered as medical devices in the following cases:

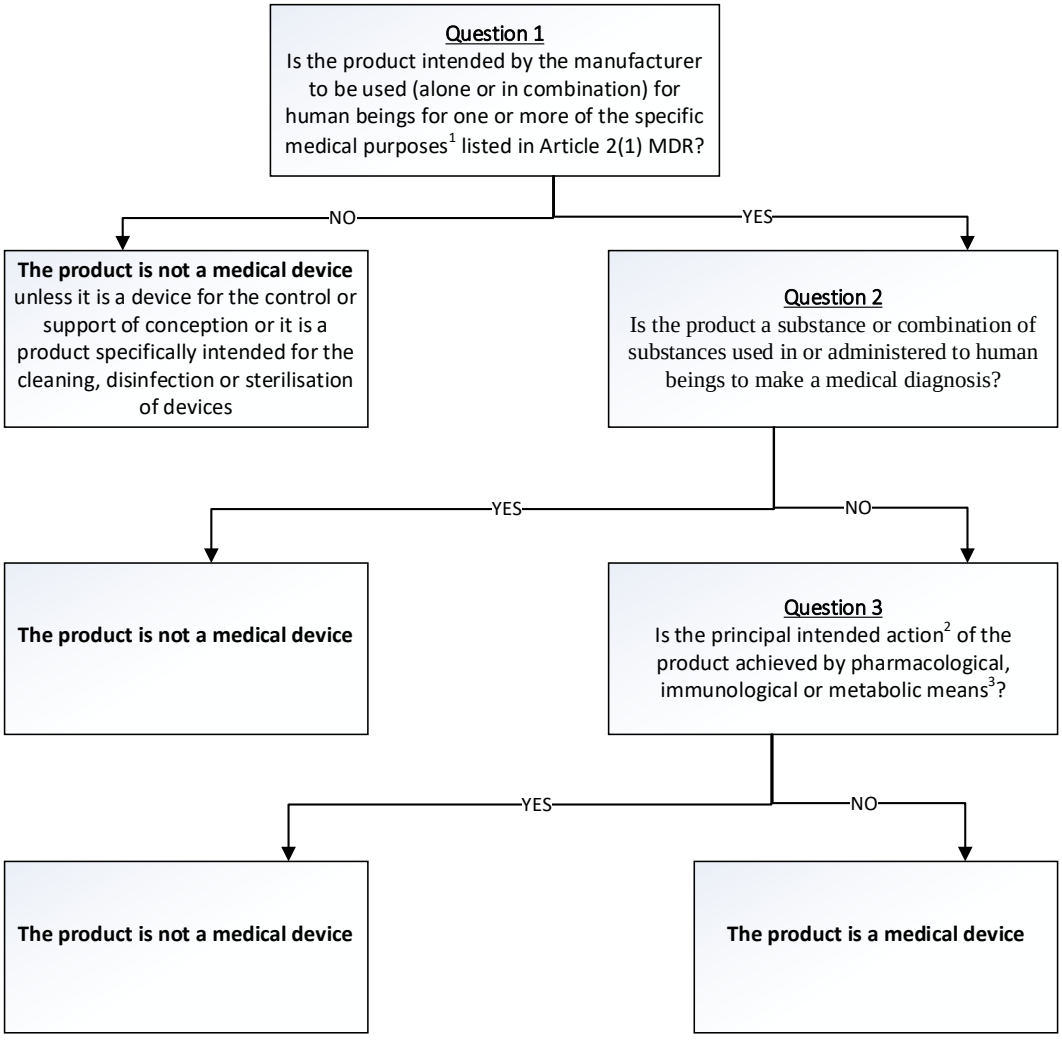
- the substance is a colorant used to mark the location of the site of the surgical procedure; the surgeon precisely marks a target area to guide a subsequent surgical act (*e.g.* endoscopic tattoo, ostomy marker);
- markers placed or implanted for radiation therapy;
- the substance is used to highlight tissues and helps to distinguish them in guiding a subsequent surgical act (*e.g.* dye in cataract surgery, fluorescence guided surgery), without the intention of making a diagnosis;
- dental impression materials;
- fluorescein strips used only for the adjustment of contact lenses; fluorescein strips intended for assessing the integrity of the cornea should not be qualified as a medical device.

Note 4: Products intended for diagnosis *in vitro* are *in vitro* diagnostic medical devices in scope of Regulation (EU) 2017/746.

1.2.4 Determining if a product fulfils the definition of a medical device

The decision tree presented below aims at assisting in determining whether a product fulfils the definition of a medical device per the MDR in order to ensure a consistent approach in the decisions concerning the borderline between medical devices and medicinal products. Such a decision requires a case-by-case assessment.

Flowchart for determining if a product fulfils the definition of a medical device



1. The specific medical purpose is specified by the manufacturer from those listed in the indents of Article 2(1) MDR.
2. The principal intended action of a medical device is described in manufacturer's labelling and claims and must be based on state of the art scientific data regarding principal mode of action, on a case-by-case basis.
3. See definitions in section 1.2.2.

1.2.5 The concepts of "a substance which, if used separately, would/may/can be considered a medicinal product" and "and that has an action ancillary to that of the device"

Directive 93/42/EEC on medical devices (MDD) contained the following provisions:

Article 1(4) '*Where a device incorporates, as an integral part, **a substance which, if used separately, may be considered to be a medicinal product** within the meaning of Article 1 of Directive 2001/83/EC **and which is liable to act upon the body** with **action ancillary to that of the device**, that device shall be assessed and authorized in accordance with this Directive.*' *[emphasis added]*

Article 1(4a) '*Where a device incorporates, as an integral part, **a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma** within the meaning of Article 1 of Directive 2001/83/EC **and which is liable to act upon the human body** with **action ancillary to that of the device**, hereinafter referred to as a 'human blood derivative', that device shall be assessed and authorised in accordance with this Directive.*' *[emphasis added]*

Annex IX, 4.1 Rule 13 '*All devices incorporating, as an integral part, **a substance which, if used separately, can be considered to be a medicinal product**, as defined in Article 1 of Directive 2001/83/EC, **and which is liable to act on the human body** with **action ancillary to that of the devices**, are in Class III.*' *[emphasis added]*

The corresponding provisions of the MDR are written in a similar manner but the element of 'and which is liable to act on the human body' has not been retained by the legislators. However, the concepts of 'a substance which, if used separately, would/may/can be considered a medicinal product' and 'and that has an action ancillary to that of the device' continue to be used. In this document the words 'would/may/can' are used differently due to different wording in various places in the MDR. Nonetheless, they are presumed to be equivalent.

The definition of 'a substance which, if used separately, would/may/can be considered to be a medicinal product' is provided in the MDR by reference to point 2 of Article 1 of MPD, including reference to a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of this Directive.

This section aims to clarify the relation between the concept of 'a substance which, if used separately, would/may/can be considered a medicinal product' and

1. the intention of the manufacturer for the presence of that substance in the device,
2. the quantity of such a substance in the device.

Article 1(8) of the MDR states that *'Any device which, when placed on the market or put into service, incorporates, as an integral part**, a substance which, if used separately, would be considered to be a medicinal product** […], **and that <u>has</u> an action ancillary to that of the device**, shall be assessed and authorised in accordance with this Regulation.' [emphasis added]*

Annex VIII, Rule 14 makes use of the same concept '*Rule 14: All devices incorporating, as an integral part, **a substance which, if used separately, can be considered to be a medicinal***

***product**, […], **and that <u>has</u> an action ancillary to that of the devices**, are classified as class III.' [emphasis added]*

Furthermore, Annex IX section 5.2(a), also applicable for Annex X section 6, requires that *'Where a device incorporates, as an integral part, **a substance which, if used separately, may be considered to be a medicinal product** […] **and that <u>has</u> an action ancillary to that of the device**, the quality, safety and usefulness of the substance shall be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC.' [emphasis added].*

The following subsections deal in turn with the two concepts of "a substance which, if used separately, would/may/can be considered a medicinal product" and "and that has an action ancillary to that of the device".

1.2.5.1. The concept of 'a substance which, if used separately, would/may/can be considered a medicinal product'

The MDR does not state that the 'substance integral to the device which, if used separately, would/may/can be considered a medicinal product', must, when in or released from the device, be intended by the manufacturer to act in or on the body, in order to be considered a medicinal product.

The substance can be considered a medicinal product regardless of whether or not it will be available to the body and regardless of its quantity in the device, the method or route of administration, due to the mention of 'if used separately'. Furthermore, the intention of the manufacturer regarding the action of the substance on the device or on the body is irrelevant for the decision on whether the substance would be considered a medicinal product, because intentionality is not mentioned in the MDR legal provisions under discussion.

It should be noted that according to point 6.2. (a) of the Annex II to the MDR, the technical documentation will contain the data of the tests conducted to assess the safety, quality and usefulness of the substance which, if used separately, may be considered to be a medicinal product and is incorporated in the device. Furthermore, according to point 5.2. (b) of the Annex IX to the MDR, the notified body performing the conformity assessment will verify the usefulness of the such substance part of the device before issuing an EU technical documentation assessment certificate, or an EU type-examination certificate under the provisions of point 6 of the Annex X to the MDR.

1.2.5.2. The concept 'and that has an action ancillary to that of the device'

The use of this concept has two sets of consequences:

- firstly, on the determination of the regulatory status of a product under Article 1(8), as the action of the 'substance which, if used separately, would be considered a medicinal product' will determine the regulatory framework which governs the product, i.e. MDR or MPD;
- secondly, on the application of certain requirements of the MDR such as a higher classification under Rule 14 and the consultation procedure under Annex IX section 5.2.

The term 'ancillary' is not defined as such in the MDR but it generally means 'providing necessary support to the primary activities or operation of an organization, system, etc.'[7].

The legislators didn't retain the concept **'and which is liable to act upon the body with action ancillary to that of the device'** and replaced it with **'has an action ancillary to that of the device'**, thus going from possibility (liable to) to obligation (has) with regard to the ancillary action of the substance.

The action of the substance has to be scientifically objective and therefore the intention of the manufacturer is not relevant for the decision as to whether the substance has an action ancillary to that of the device. In line with this, intentionality is not mentioned in the MDR legal provisions under discussion.

An action of the substance ancillary to that of the device should be understood as taking place in or on the human body or its constituents (e.g. blood, organs, *in vivo* or *ex viv*o, gametes, exudate from a wound) and supporting the device in achieving its specific medical purpose. For example, if a substance is shown not to be available to the human body or its constituents, e.g. fixed in the matrix of the device without leaching or without surface interaction with the body or its constituents, then it is considered that it would not have an action ancillary to that of the device. For consideration whether the substance has an action ancillary to that of the device, the quantity that is available to the human body or its constituents should be taken into account. For example, if the substance is shown by the manufacturer to be available to the human body or its constituents in such a quantity that it does not have an action in or on the human body or its constituents, then it is considered that it would not have an action ancillary to that of the device.

Examples of substances, which, if used separately can be considered a medicinal product and may be available to the human body or its constituents, but might not have an action ancillary to that of the device due to the quantity available to the body or its constituents, as demonstrated by the manufacturer, may include substances used as flavourings, colorants, antioxidants or chelating agents, provided that they do not have any other type of action in or on the human body or its constituents which is ancillary to that of the device after being administered.

If the manufacturer shows that the substance does not have any action ancillary to that of the device, no claims of benefits pertaining to that substance may be made on the IFU, labelling, packaging, advertising and websites or through any other means of communication (Article 7 MDR).

It falls under the obligations of the manufacturer to demonstrate whether or not the substance has any action ancillary to that of the device based on state of the art scientific data. A simple claim would not be sufficient. The inclusion of a substance which would be considered a medicinal product which assists or, where not supported by evidence to the contrary provided by the manufacturer, could possibly assist the device in its action, constitutes the inclusion of a substance with ancillary action.

[7] https://www.lexico.com/definition/ancillary

To conclude

The determination of the nature of the substance, i.e. whether it is "considered to be a medicinal product" is independent of the intention of the manufacturer, of the quantity of the substance in the device and of the method or route of administration. Also, the determination of whether the substance "has an action ancillary to that of the device" is scientifically objective and does not depend on the manufacturer's intention for the action of that substance in the device. Determining whether the substance "has an action ancillary to that of the device" should take into account the availability of the substance to the human body or its constituents and/or the quantity that is available to the human body or its constituents. It falls under the obligations of the manufacturer to demonstrate whether or not the substance has any action ancillary to that of the device, based on state of the art scientific data. A simple claim would not be sufficient.

The same approach should be used for the application of Rule 14 of Annex XVIII to the MDR.

1.2.6 Examples

1.2.6.1 Examples of medical devices

The following examples should, in view of their principal mode of action, generally be considered as medical devices subject to the relevant criteria being met; the function of some of the devices indicated in these examples may be assisted by the presence of medicinal product where such substances have an ancillary action to that of the device.

- Bone cements
- Dental filling materials
- Materials for sealing, approximation, or adhesion of tissues (*e.g.* cyanoacrylates, fibrin-based adhesives)
- Resorbable materials used in osteosynthesis (*e.g.* pins or bone screws manufactured using polylactic acid)
- Sutures, absorbable sutures
- Soft and hard tissue scaffolds and fillers (*e.g.* calcium phosphate, bioglass)
- Bone void fillers intended for the repair of bone defects where the principal mode of action of the device is physical (*e.g.* matrix which provides a volume and a scaffold for osteoconduction)
- Intrauterine devices, except products such as intrauterine contraceptives intended to release progestogens
- Blood bags
- Plasmapheresis systems
- Gases and liquids for ocular endotamponades
- Cell separators, including those incorporating fixed antibodies for cell binding
- Wound dressings, which may be in the form of liquids, gels and pastes, etc (*e.g.* hydrocolloid, hydrogel)
- Haemostatic products, *e.g.* patches, plugs and powders where the haemostatic effect results from the product's physical characteristics, or is due to the surface properties of the material.

This includes products such as calcium alginate or oxidised cellulose where adhesion of platelets to the surface triggers platelet adhesion and aggregation

- Concentrates for haemodialysis
- Pressure reducing valves and regulators
- Irrigation solutions intended for mechanical rinsing (*e.g.* bladder irrigation solution, ocular irrigation solution)

Note: If the solution contains a medicinal product whose action is principal, such as, for example, chlorhexidine where the principal intended action is to provide a local antimicrobial effect, it will be a medicinal product. Solutions incorporating substances with ancillary action, *e.g.* preservatives, remain a medical device.

- Devices such as catheters, guidewires and stents containing or incorporating radio isotopes where the radioactive isotope as such is not released into the body, used for example in cardiology for the prevention of restenosis
- Products specifically intended for the cleaning, disinfection or sterilisation of medical devices, including during the manufacture of the devices (*e.g.* ethylene oxide for sterilisation of endoscopes)

Note: Multipurpose disinfectants or sterilisation agents which are not specifically intended by their manufacturer for the disinfection or sterilisation of medical devices are not covered by the MDR; they are covered by the Regulation (EU) 528/2012 on biocidal products.

1.2.6.2 Examples of accessories of medical devices

The following products fall under the definition of "accessory":

- Contact lens care products (rinsing and hydrating solutions including those which aid the insertion and/or wearing of contact lenses without therapeutic claim)
- Lubricants specifically intended for use together with medical devices (*e.g.* for gloves, endoscopes, condoms)
- Skin barrier powders and pastes or other skin care products specifically intended for use together with ostomy bags
- Gases used to drive cryoprobes and surgical tools
- Ultrasound gels

1.2.6.3 Examples of medicinal products:

The following examples should generally be considered as medicinal products subject to relevant criteria being met:

- Spermicidal preparations
- Gases intended to be used in anaesthesia and inhalation therapy, (e.g. oxygen, medical air supplied in containers) including their primary containers

Note: These gases are also used in minimal access surgery. However, a product intended exclusively for minimal access surgery with a physical mode of action (*e.g.* inflation) would be a medical device.

- Disinfectants for use on non-intact skin or on the patient before a surgical procedure

- Haemostatic and sealant products interacting with the coagulation cascade through pharmacological means (such as collagens which have a molecular structure capable of surface independent demonstrated interaction with platelet receptors)
- Water for injections, IV fluids and other fluids for intramuscular injection and plasma volume expanders
- *In vivo* diagnostic agents, *e.g.* x-ray contrast media, NMR enhancing agents, fluorescent ophthalmic strips for diagnostic purposes, radiopharmaceuticals for diagnostic use
- Gases for *in vivo* diagnostic purposes, including lung function, tests, *e.g.* carbon dioxide for vascular diagnostic purposes
- Fluoride dental preparations where the action of fluoride is not ancillary[8]
- Products containing peppermint oil or menthol with intended medical purposes such as the relief of discomfort and pain in muscles and joints, relief of back pain, etc. as their principal mode of action is pharmacological involving interaction with the cold-sensitive receptors in the skin
- Radiopharmaceuticals used for treatment or diagnosis

2. HERBAL PRODUCTS

2.1 Definitions of a herbal medicinal product and traditional herbal medicinal product

Herbal medicinal product (article 1 (30) MPD)*:* Any medicinal product, exclusively containing as active ingredients one or more herbal substances (article 1 (31) MPD) or one or more herbal preparations (article 1 (32) MPD), or one or more such herbal substances in combination with one or more such herbal preparations.

A herbal medicinal product may be licensed under 3 different Articles of the MPD, and in particular article 16(a) regarding traditional use is a common avenue for this purpose, and requires that the herbal medicinal product complies with several conditions including sufficient data on traditional use, namely that the pharmacological effects or efficacy of the medicinal product are plausible on the basis of longstanding use and experience.

Traditional herbal medicinal product (Article 1 (29) MPD): A herbal medicinal product that fulfils the conditions laid down in Article 16a(1).

Since herbal medicinal products are usually multicomponent mixtures, if the pharmacodynamics are unknown, the principal mode of action could be difficult to define. So in case of doubt, if it is not clear which substance is responsible for the principal intended action of the product or if it is achieved by pharmacological, immunological or metabolic means, Article 2(2) of Directive 2004/27/EC amending Directive 2001/83/EC will apply and the product will be considered as a medicinal product.

Note: It should be noted that Directive 2004/24/EC on traditional herbal medicinal products has been introduced as an appropriate legal framework for such herbal medicinal products that have a long-standing tradition in the EU, but do not fulfil the requirements of a well-established medicinal use with recognized efficacy and acceptable level of safety and therefore are not

[8] See also Regulation (EC) 1223/2009 on cosmetic products. https://ec.europa.eu/growth/sectors/cosmetics/legislation_en

eligible for a full marketing authorisation application. The term 'traditional herbal medicinal product' is defined, as amended, in Art 1 (29) of Directive 2001/83/EC. For traditional herbal medicinal products the pharmacological effects or efficacy of the product are considered plausible on the basis of long-standing use and experience. A product that fully complies with the legal definition of a traditional herbal medicinal product is a medicinal product.

To facilitate the harmonisation of the process of authorisation and registration for (traditional) herbal medicinal products in the European Union, there are EU monographs (established by the EMA Committee on Herbal Medicinal Products - HMPC) for certain herbal substances and preparations. To help in the qualification of some products, these monographs should be taken into account. Also other official monographs such as the German Commission E monographs, ESCOP (European Scientific Cooperative on Phytotherapy), or WHO (World Health Organization) monographs, may be considered. Even though only HMPC herbal monographs carry legal value in the authorisation process, when a substance included in these monographs complies with the monograph regarding its composition/preparation, dosage and indication, it is a good indicator that the substance in question falls into the definition of herbal medicinal product. However the fact that a monograph does not exist for a herbal substance in one of the abovementioned pharmacopoeias does not necessarily mean that it shall not be considered a herbal medicinal product. In such cases, the mode of action of the substance needs to be carefully examined. So, a substance cannot be excluded as a herbal medicinal product simply because it is not included in the abovementioned documents.

If it is demonstrated by the manufacturer that a substance with plant origin achieves its principal intended action by means other than pharmacological, immunological or metabolic, then the respective product should be qualified as a medical device if it fits the definition under Article 2(1) MDR. For further considerations see below and Section 1.2.2.

However, it is also possible that a product containing herbal substance(s) and/or herbal preparation(s) that have a demonstrated pharmacological action could be qualified as a medical device, if the action of the herbal constituent is ancillary and the principal intended action of the product is achieved by physical or mechanical means. In this case, all relevant regulatory provisions apply. Manufacturers should provide solid state of the art scientific data to demonstrate the principal mode of action. A product containing a herbal substance is not automatically a medicinal product or a traditional herbal medicinal product.

Also, the classification principles relating to medical devices incorporating as an integral part a substance which, if used separately, would be considered to be a medicinal product remain the same irrespective of whether the medicinal product is a 'conventional' or a 'herbal' medicinal product which has been authorised by a full dossier application, specific authorisation dossiers or traditional use.

2.2 Examples of herbal medicinal products[9]:

The examples listed below should generally be considered as herbal medicinal products subject to relevant criteria being met. They are based on medicinal products available on some EU Member States' markets.

- **Cough syrup**
  Composition:
  Cetraria islandica L., (Icelandic Lichen); *Malva sylvestris* L. (Mallow flower)
  Cetraria islandica (Icelandic Moss / Lichen) has been traditionally used for its anti-bacterial and anti-inflammatory properties
  Malva sylvestris (Mallow flower) has been traditionally used as an expectorant and also as anti-inflammatory
  Claims: Treatment of irritation of the oral and pharyngeal mucosa, accompanied with dry, irritating cough.

- **Aftersun ointment for skin inflammations, treatment of wounds and sunburns**
  Composition: *Calendula officinalis* L., flos (calendula flower). *Calendula* is traditionally used for skin and mucous membrane inflammations, to treat wounds, burns and sunburns. Antimicrobial, anti-inflammatory and wound healing effects have been demonstrated for various different extracts.
  Claims: Treatment of minor inflammations of the skin (such as sunburn).

- **Wound healing ointment**
  Composition: *Echinacea purpurea* (L.) Moench, herba recens (purple coneflower herb) *Echinaceae* is traditionally used for a wide range of conditions, namely externally, for wounds, burns and insect bites. Immunomodulatory and antimicrobial effects have been demonstrated.
  Claims: Treatment of small superficial wounds.

- **Intrarectal ointment**
  Composition: *Hamamelis virginiana* L., cortex (hamamelis bark). *Hamamelis* preparations have been traditionally used as an astringent and anti-inflammatory for mild skin injuries, haemorrhoids, varicose veins and local inflammations of the skin and mucous membranes.
  Claims: Relief of symptoms associated with haemorrhoids, such as itching, burning sensation.

- **Vaginal ovules A**
  Composition: *Calendula officinalis* extract; *Malva sylvestris* extract; *Tilia tormentosa* extract. Calendula is traditionally used for skin and mucous membrane inflammations, to treat wounds, burns and sunburns. Antimicrobial, anti-inflammatory and wound healing effects have been demonstrated for various different extracts.

[9] Please note that the following examples identify some actions attributed to the relevant herbal active substances. Nevertheless, these examples do not identify all actions of the relevant herbal substances in a comprehensive manner and therefore these substances could have additional actions and be used for different medical purposes not identified in this guidance.

Malva sylvestris has been traditionally used as an expectorant and also as anti-inflammatory.
Tilia tomentosa is not the *Tilia* species that is normally used (and has a monograph in the European Pharmacopoeia). However, traditionally, Lime flower has been traditionally used as sedative, antispasmodic, diaphoretic, diuretic and mild astringent.
Claims: Vaginal ovules with soothing, protective and refreshing action with slightly alkaline pH, specially formulated to relieve vaginal itching. With efficient symptomatic anti-itch action.

- **Vaginal ovules B**
  Composition: *Chamomilla recutita* extract; *Lavandula angustifolia* extract.
  Chamomilla recutita is traditionally used as an anti-inflammatory (mainly local), spasmolytic, carminative and stomachic. Several activities (like the antiphlogistic, spasmolytic, ulcer protective, bactericidal, and fungicidal activities) have been demonstrated.
  Lavandula angustifolia - it has 1-3% essential oil (according to Ph. Eur., not less than 1.3%). Also contains tannins, flavonoids, traces of phytosterols and triterpenes. Lavender essential oil has been traditionally used for its antimicrobial and sedative activities.
  Claims: Vaginal ovules with protective, healing, lubricating and softening action. Intended for use in cases of vaginal dryness, even if it causes itching, reddening and irritations. Especially recommended as vaginal lubricants, during the climacteric period (pre-menopause, menopause, post-menopause).

- **Intrarectal ointment**
  Composition: *Helichrysum italicum* extract; *Ruscus aculeatus* extract (Butcher's Broom root).
  Helichrysum italicum – it is traditionally used as an expectorant, antitussive, choleretic diuretic anti-inflammatory and antiallergic agent.
  Ruscus aculeatus (butcher's broom) – it is traditionally used for haemorrhoids, feeling of heaviness in the legs, pruritus and swelling. Supportive therapy for complaints of haemorrhoids, such as itching and burning.
  Claims: Relief of haemorrhoid ailments. Treatment of the varicose haemorrhoidal syndrome (internal and external haemorrhoids) and anal fissures. Prevention of perianal irritation and congestion, providing relief from local pain, pruritus and burning sensations.

- **Analgetic gel: cutaneous gel for local anaesthesia**
  Composition: *Helichrysum italicum* water; *Eugenia caryophyllus* Oil; *Arnica montana* extract; *Harpagophytum procumbens* extract; *Zingiber officinale* extract (Ginger); *Boswellia serrata* extract; *Cinnamon cassia* oil; *Helichrysum italicum* oil; *Urtica dioica* extract; *Boswellia carterii* oil – Olibanum (more popularly known as frankincense).
  Helichrysum italicum – it is traditionally used as an expectorant, antitussive, choleretic diuretic antiinflammatory and antiallergic agent.
  Eugenia caryophyllus – volatile oil has been traditionally used for its local anaesthetic properties.

Arnica montana is traditionally used for its topical counter-irritant and anti-inflammatory properties.
Harpagophytum procumbens has been traditionally used for its anti-inflammatory and analgesic properties in arthritis, gout, myalgia, fibrositis, lumbago, pleurodynia and rheumatic disease.
Zingiber officinale. Ginger is traditionally used for its carminative, diaphoretic and antispasmodic properties.
Cinnamon cassia – Carminative and antiseptic properties are documented for the oil.
Urtica dioica has been traditionally used for uterine haemorrhage, cutaneous eruption, infantile and psychogenic eczema, epistaxis, melaena and specifically for nervous eczema.
Boswellia serrata, Boswellia carterii – has been traditionally used as a stimulant, respiratory antiseptic, diuretic and emmenagogue, for rheumatism and as a topical antiinflammatory.
Claims: local anaesthesia

3. SUBSTANCE-BASED MEDICAL DEVICES

3.1 General principles

A substance-based medical device is a medical device which:

- is composed of substances that are permitted in a medical device, and
- does not achieve its principal intended action by pharmacological, metabolic or immunological means.

Note: there may be ancillary pharmacological, metabolic or immunological action of one or more of the substance(s) the device is made of. See Section 1.2.2 for the definitions of pharmacological, immunological and metabolic. The assessment of the ancillary nature of the pharmacological, immunological or metabolic action of such substances is a crucial element for the qualification of the product as a medical device.

Such devices may be similar in formulation to a medicinal product and may also be used in a similar way to a medicinal product *e.g.* ingested or applied to the skin.

'**Substance'** is not defined in the MDR. Although a definition is contained in the MPD (see Section 1.2.2), this definition includes substances that are not permitted in medical devices. Therefore a substance-based medical device where the substance falls under the definition in the MPD must also satisfy all other aspects of the definition of a medical device as specified in Article 1 and 2 of the MDR.

Substances that are not permitted in medical devices include, but are not limited to[10]:

- viable biological material or viable organisms, including living micro-organisms, bacteria, fungi or viruses;
- viable animal tissues or cells or their derivatives;
- viable human tissues and cells or their derivatives.

[10] See Article 1(6) MDR for the full list.

Under the MDR Annex VIII there are two classification rules applying specifically to substance-based devices that take into account the relevant risks, these are rule 3 and 21. Not all substance-based devices fall under these two rules and in that case they would be classified under the general rules.

I. Medical device consisting of a substance or mixture of substances used *in vitro* in direct contact with human cells, tissues, organs, or human embryos before their implantation or administration (classified by Rule 3, Annex VIII MDR)
II. Medical device 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 (classified by Rule 21, annex VIII MDR)
III. Other substance-based devices (no specific rule for these devices)

All other rules and requirements should also be considered. For examples, where a substance-based device incorporates a substance, which, if used separately, would be considered a medicinal product and where the action of the medicinal product is ancillary to that of the device, a consultation with a competent authority or EMA is necessary according to section 5.2 of Annex IX, MDR. See relevant MDCG guidance for further information on this consultation procedure.

3.2 Medical devices consisting of a substance or mixture of substances used *in vitro* in direct contact with human cells, tissues, organs, or human embryos before their implantation or administration

Rule 3 of Annex VIII MDR refers to devices consisting of substances that are intended to be used *in vitro*. This rule covers medical devices for extracorporeal treatment of body fluids/tissues that will eventually be reintroduced into the body. It also covers substance-based devices for use with human embryos.

3.2.1 Examples of substance-based devices for use *in vitro*:

- Solutions for the transport of organs for transplantation (that do not achieve their principal intended action via pharmacological, immunological or metabolic means),
- IVF media

3.3 Medical devices composed of substances or of combinations of substances that are intended to be introduced into the human body or applied to the skin

Products that are “composed of substances or 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” and which fulfil the definition of a medical device in MDR Art 2(1) are medical devices.

For devices that are systemically absorbed to achieve their intended purpose (Rule 21 first indent), a consultation procedure with a medicinal products competent authority or the EMA is necessary according to section 5.4 of Annex IX, MDR. See relevant MDCG guidance for further information on this consultation procedure.

3.3.1 Examples of substance-based devices intended to be introduced into the human body or applied to the skin

- Na/Mg alginate, xyloglucan
- Fat absorbers that are systemically absorbed, themselves or their metabolites
- Substance-based formulations for skin treatment
- Salt water used *e.g.* as nose or throat sprays
- Oral cough treatments that achieve their intended purpose in the oral cavity as far as the pharynx
- Simethicone preparations for oral administration
- Active coal for oral administration
- Gels for vaginal moisturizing/vaginal lubricants
- Eye drops for hydration
- Ear drops
- Medical devices for oral administration for the treatment of diarrhoea, *e.g.* kaolin, diosmectite
- Medical devices for oral administration for the treatment of obesity, *e.g.* fructooligosaccharides, glucomannan

See also section 1.2.6.1.

4. MEDICAL DEVICE AND MEDICINAL PRODUCT COMBINATIONS

4.1 Introduction

Some medical devices are intended for use with a medicinal product in different configurations.

The MDR sets out four regulatory scenarios for medical devices intended for use with a medicinal product in Article 1(8) and Article 1(9), see flow chart below.

A substance would be considered a medicinal product if it meets the definition provided in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, see Section 1.2.1.3 for further considerations.

The concept of ‘integral’ is referenced on multiple occasions within the MDR. For the scope of this document the references to Articles 1 (8) and (9) are relevant:

- integral part – Article 1(8) 1st paragraph, referring to devices incorporating a substance which, if used separately, would be considered a medicinal product.
- integral product – Article 1(8) 2nd paragraph, referring to devices incorporating a substance which, if used separately, would be considered a medicinal product.
- single integral product – Article 1(9) – 2nd paragraph, referring to devices intended to administer a medicinal product.

The following intends to clarify the meaning of 'integral':

1) '**integral'** in the context of Article 1(8) first and second paragraph**:**

A medical device incorporates one or more substances which, if used separately, would be considered a medicinal product, including medicinal products derived from human blood or plasma, non-viable tissues or cells of human origin or their derivatives as an **integral part**, within the meaning of 1(8) MDR, if and only if, the device and the substance form an **integral product**, when placed on the market or put into service.

An **integral product** consists of at least two constituent parts, one of which is a device, which are combined (e.g. physically, chemically) in such a manner that they form a single entity when placed on the market.

Note 1: if the relevant combination takes place at the time of administration, the product is not considered integral.

Note 2: medical devices co-packaged with a medicinal product, devices referenced in the medicinal product information, or medicinal products referenced in the information supplied with the device, are not considered integral products.

Note 3: the term 'putting into service' is relevant for products/components which are not placed on the market but used for complex medical devices which are assembled by the manufacturer at the hospital, e.g. central gas supply, linear accelerator.

2) '**integral'** in the context of Article 1 (9) second paragraph:

A device intended to administer a medicinal product and the respective medicinal product form a **single integral product**, within the meaning of Article 1 (9) of MDR, if and only if the device and the medicinal product form an integral entity when placed on the market and, furthermore, the product is intended exclusively for use in the given combination and which is not reusable.

A **single integral product** consists of at least two constituent parts, one of which is a device and the other a medicinal product, which are combined in such a manner that they are not intended to be separated prior to administration.

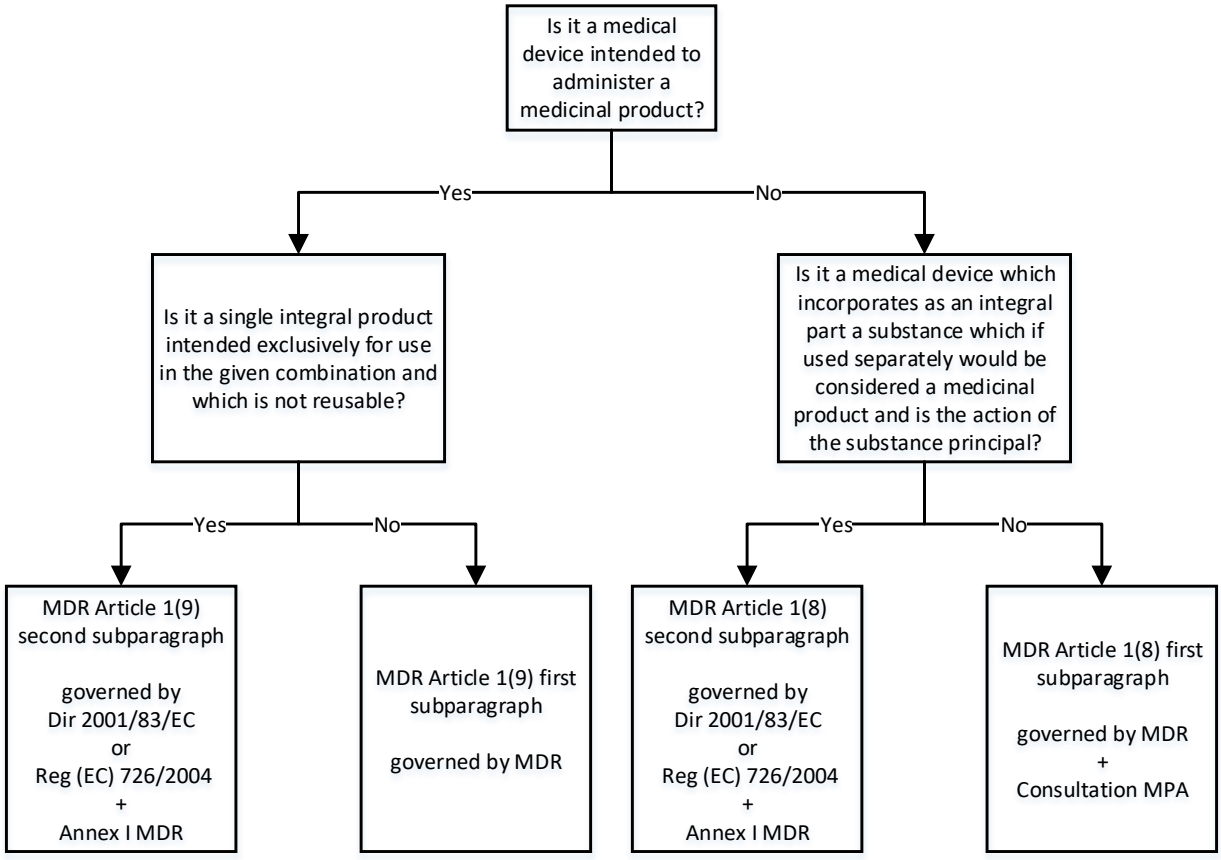
Note: medical devices which are co-packaged with medicinal products or referenced in the medicinal product information leaflet and are not 'integral' or 'single integral' products are not considered combination products (in the meaning of Recital (10) MDR) or drug-device combinations and are regulated independently.

When deciding on the regulatory status of a product combination, the first step is establishing whether the product under consideration is an integral product according to the explanations provided above. As a second step, it should be determined if the action of the medicinal product incorporated in the device is principal or ancillary to that of the device part of the integral product.

If the principal intended action of the integral product is achieved by the substance, the entire product is regulated as a medicinal product under Directive 2001/83/EC or Regulation (EC) No 726/2004, however if the principal intended action is achieved by the medical device

the entire product is regulated under the MDR as a medical device incorporating a medicinal product that has an action ancillary to that of the device. Devices for administration of medicinal products where the medicinal product is supplied separately (Article 1(9) first paragraph) are not integral products.

Flowchart for determining the regulatory status of combination products



4.2 Medical device and medicinal product integral combinations regulated as medicinal products

This category includes devices that are intended to administer a medicinal product and where the device and the medicinal product form a single integral product, which is intended exclusively for use in the given combination and which is not reusable (Article 1(9) second subparagraph, MDR). It also covers devices that incorporate, as an integral part, a medicinal product where the action of the medicinal product is principal relative to that of the device (Article 1(8) second subparagraph, MDR).

According to the MDR, the integral product is governed by the Directive 2001/83/EC or by Regulation (EC) No 726/2004 but the relevant general safety and performance requirements of Annex I to the MDR shall apply as far as the safety and performance-related device features are concerned.[11] If the device is CE marked, the results of the conformity assessment shall be

[11] Articles 1(8) MDR second subparagraph and 1(9) MDR, second subparagraph.

included in the marketing authorisation dossier, including variation dossier, (conformity assessment results covering the relevant general safety and performance requirements set out in Annex I of the MDR contained in the manufactures EU declaration of conformity or the valid CE certificate issued by a notified body), however, if the dossier does not include this information, and if conformity assessment of the device, if used separately, would require the involvement of a notified body, an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I issued by a notified body designated, for the type of device, in accordance with the MDR should be provided. Further guidance is available from the EMA.[12]

4.2.1 Examples of medical device and medicinal product integral combinations regulated as medicinal products

- Syringes prefilled with a medicinal product
- Aerosols containing a medicinal product
- Nebulisers pre-charged with a specific medicinal product
- Patches for transdermal drug delivery
- Implants containing medicinal products in a polymer matrix whose purpose is to release the medicinal product, for example plastic beads containing antibiotic for treating bone infections, or a matrix to release osteoinductive proteins into the surrounding bone
- Intrauterine contraceptives whose purpose is to release progestogens
- Single-use disposable iontophoresis devices incorporating a medicinal product, whose purpose is to deliver the medicinal product for the treatment of a medical condition
- Wound treatment products comprising a matrix whose purpose is the administration of medicinal products, for example wound dressings containing an antimicrobial agent where the primary action of the dressing is to administer the agent to the wound for the purpose of controlling infection
- Temporary root canal fillers incorporating medicinal products, whose purpose is to deliver the medicinal product
- Tablets containing a medicinal product with embedded sensor to monitor adherence to treatment

4.3 Medical device for administration of medicinal products

This category concerns devices that are intended to administer a medicinal product within the meaning of the MPD where the device and the medicinal product are not integral.

In this case, that device is governed by the MDR without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product.[13]

4.3.1 Examples of medical devices for administration of medicinal products

- Drug delivery pumps
- Implantable infusion pumps
- Reusable iontophoresis devices

[12] https://www.ema.europa.eu/en/quality-documentation-medicinal-products-when-used-medical-device https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/questions-answers-implementation-medical-devices-vitro-diagnostic-medical-devices-regulations-eu/745-eu-2017/746_en.pdf

[13] Article 1(9) MDR first paragraph

- Nebuliser
- Syringes, jet injectors
- Spacer devices for use with metered dose inhalers
- Port systems

4.4 Medical devices incorporating, as an integral part, an ancillary medicinal product

The MDR specifies the case of medical devices incorporating, as an integral part, a substance which, if used separately, would be considered to be a medicinal product according to Article 1 of the MPD, including a medicinal product derived from human blood or human plasma, with an action ancillary to that of the device.[14] For brevity, these are referred to in this document as devices incorporating, as an integral part, an ancillary medicinal product. This includes also herbal medicinal products.

Such devices shall be assessed and certified in accordance with the MDR.

4.4.1 Examples of medical devices incorporating, as an integral part, an ancillary medicinal product

The following list contains examples of devices which incorporate an ancillary medicinal product:

- Catheters coated with heparin or an antibiotic agent
- Bone cements containing antibiotic
- Root canal fillers which incorporate medicinal products with ancillary action to that of the device
- Soft tissue fillers incorporating local anaesthetics
- Bone void filler containing growth factors
- Condoms coated with spermicides
- Electrodes with steroid-coated tip
- Wound dressings, surgical or barrier drapes (including tulle dressings) with antimicrobial agent
- Intrauterine contraceptives containing copper or silver
- Ophthalmic irrigation solutions principally intended for irrigation which contain components that support the metabolism of the endothelial cells of the cornea
- Drug eluting coronary stents
- Blood bags containing substances which, if used separately, would be considered to be a medicinal product
- A liquid wound dressing with antimicrobial agent.

Note: It should be noted that the mere coating of a product with a chemical does not imply that the substance is a medicinal product. For example, hydroxyapatite, frequently used as coating for orthopaedic and dental implants, is not considered a medicinal product. Other coatings which are in use and which are not medicinal products are hydromers and phosphorylcholines.

[14] Article 1(8) MDR.

The following are examples of herbal substances considered to be medicinal products and therefore, when included/incorporated in a medical device, this may lead to classification as a class III medical device according to rule 14 of Annex VIII of Regulation (EU) 2017/745. In such cases the manufacturer must demonstrate that the action is ancillary to the principal intended action of the device[15].

- Yerba Santa (*Eriodictyon californicum*) - used via oral route for asthma, bronchitis, laryngitis, sinusitis and hay fever
- Clove Oil (*Caryophylli aetheroleum*) - has antiseptic analgesic and sedative properties,
- Mallow (*Malva silvestris*) - anti-inflammatory properties
- Icelandic Moss / Litchen (*Cetraria islandica*) - anti-bacterial and anti-inflammatory properties
- *Calendula officinalis* (Marigold) - anti-inflammatory and antiseptic properties
- *Lavandula angustifolia* (Lavender) - antiseptic properties
- Chamomile (*Chamomilla recutita*) - anti-inflammatory, antiseptic and spasmolytic action, pain relief
- Butchers Broom (*Ruscus aculeatus* root) - used in the treatment of haemorrhoids, helps reduce inflammation and is used as a laxative
- St Johns Wort (*Hypericum* perforatum) - anti-inflammatory, antiseptic and analgesic properties
- *Alchemilla vulgaris* (Alchemilla / Lady's Mantle) - has anti-inflammatory and astringent properties
- Eriodictyon (*Eriodictyon crassifolium*) - used for saliva production, pulmonary conditions and to stop bleeding
- *Thymus vulgaris* (Thyme) - disinfectant, antiseptic and expectorant properties
- *Foeniculum vulgaris* (Fennel) - various medicinal uses
- *Salvia officinalis* (Sage) - antibiotic and antifungal properties

4.4.2. Examples of medical devices incorporating, as an integral part, a human blood or human plasma derivative

- Haemostatic agent / matrix containing human thrombin
- Culture media used in IVF containing human albumin solution

[15] The default assumption when herbal substances are used is that these substances will have at least an ancillary effect to the device. If the herbal substance is used with a different purpose, like perfume or flavour, the manufacturer should provide scientific evidence that the substance does not have an ancillary action to the device in question.