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To cite this article: Marco Racchi, Stefano Govoni, Adele Lucchelli, Laura Capone & Emiliano Giovagnoni (2016): Insights into the definition of terms in European medical device regulation, Expert Review of Medical Devices, DOI: [10.1080/17434440.2016.1224644](https://doi.org/10.1080/17434440.2016.1224644)

To link to this article: <http://dx.doi.org/10.1080/17434440.2016.1224644>



Accepted author version posted online: 13 Aug 2016.  
Published online: 25 Aug 2016.



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REVIEW

## Insights into the definition of terms in European medical device regulation

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### ABSTRACT

**Introduction:** Medical devices comprise apparatus/instruments, software, and materials with therapeutic activities obtained by principal mechanisms of action different from pharmacological, immunological and metabolic, which are proper of medicinal products. In this context the key for the distinction between medicinal products and devices lies in the correct interpretation of these terms, which, although defined in a guideline, are still not univocally interpreted.

**Areas covered:** This article discusses the definitions of pharmacological and non-pharmacological mechanisms of action, such as the chemical and physical means. The aim is to give insights on the correct definition these terms in order to contribute to build the desired synergy between scientific and regulatory fields and promote a correct interpretation of the European regulatory framework as well as sustainable health and innovation.

**Expert commentary:** We propose a series of definitions and a method to interpret those definitions within possible decision tree paradigm. Specifically, we propose to define the difference between the terms 'action' of a medical device compared to the 'mechanism of action' of such device. In any decisional procedure the correct interpretation of these and other correlated terms is needed to correctly assess whether a substance is a medicinal product or a medical device.

### ARTICLE HISTORY

Received 12 July 2016  
Accepted 11 August 2016  
Published online  
25 August 2016

### KEYWORDS

Medical device regulation; mechanism of action; therapeutic effect; pharmacological mechanism; immunological mechanism; metabolic mechanism; regulatory definitions

## 1. Introduction

Medical devices are very wide-ranging products, such as apparatus/instruments, software, and materials (i.e. substances). Various definitions for the expression 'medical device' coexist according to regulations in the United States, European Union (EU), and Japan. Overall, the term refers to any apparatus, software, material, or other similar or related item intended to be used in the diagnosis, prevention, monitoring, treatment or alleviation of a disease or injury. Within these definitions and in spite of minor differences the phrasing regarding the 'primary intended action' of a medical device is currently responsible for the increasing number of products that are in the borderline between devices and drugs [1], and most of the controversies arise from the interpretation of the definition of terms, such as 'pharmacological, immunological, and metabolic mechanism of action'. We intend to discuss these definitions within the EU legislation.

The key for the distinction between medicinal product (drug) and medical device, therefore, lies in the interpretation of the main concepts that define them: therapeutic effect and mechanism of action. Medical devices and medicinal products share the common essence of having a therapeutic effect, while they are different for the mechanism of action with which they reach their effect. Medicinal products have a pharmacological (Ph.), immunological (I), or metabolic (M) mechanism of action, while medical devices have non-Ph.I.M. mechanisms. In case of devices, which look like medicinal products for their external presentation, such as substance-based medical devices, three main aspects create confusion, as of today: (1) the definition of medicinal product before 2004 overlapped with that of medical device; (2) the

concepts of 'therapeutic effect' and 'mechanism of action' are often confused or wrongly considered to be equivalent; (3) specific considerations on the essential features of the 'pharmacological, immunological, and metabolic modes of action' and on the 'non-pharmacological, immunological, and metabolic modes of action', such as the chemical and physical modes of action, have not been clearly described, giving rise to possible controversy.

## 2. General definitions

In Table 1 and the subsequent paragraphs, we list the initial and the current definitions of the two product categories, and briefly address their regulatory evolution.

### 2.1. Definition of medicinal product

The definition of medicinal product was issued originally in Directive 65/65/EEC [2] and proceeded to the definition given in Directive 2001/83/EC [3] subsequently amended by Directives 2004/24/EC [4] and 2004/27/EC [5]. In time, the definitions became increasingly specific in character: while in the original 1965 document the definition of medicinal product involved the presentation and the therapeutic purpose of the product (i.e. to act on altered physiological functions), the current definition specifies the type of action a substance must exert to be considered a medicinal product.

In the first above-mentioned regulatory documents, the definitions relate particularly to the purpose of use of the product. The medicinal product has the purpose of treating or preventing

**Table 1.** Timeline of the definitions of medicinal product (a) and medical device (b).

(a) Medicinal product		
Dates	European directives	Definition
1965	Directive 65/65/EEC	Medicinal product: any substance or combination of substances presented for treating or preventing disease in human beings or animals Any substance or combination of substances, which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product  <i>Comment: Only the presentation and purpose of the medicinal product are addressed, without specifying the mechanism of action.</i>
2001	Directive 2001/83/EC	Medicinal product: any substance or combination of substances presented for treating or preventing disease in human beings Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product  <i>Comment: Prior to the 2004 amendments, the definition does not include the mechanism of action of the medicinal product as a fundamental element for product classification. Thus, despite the fact that the Medical Device Directive had already been issued, the definition of medicinal product did not yet address complementary mechanisms of action in medical devices and medicinal products. 'Animals' is deleted, in view of the upcoming Veterinary Medicinal Products Directive.</i>
2004	Directive 2004/27/EC	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.  <i>Comment: Medicinal products are now characterized not only by presentation but also by capacity to modify physiological functions via a specific mechanism of action: pharmacological, immunological, or metabolic.</i>
(b) Medical device		
Dates	European directives	Definition
1993	Directive 93/42/EEC	Medical device means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:  <ul style="list-style-type: none"> <li>• diagnosis, prevention, monitoring, treatment, or alleviation of disease</li> <li>• diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap</li> <li>• investigation, replacement, or modification of the anatomy or of a physiological process</li> <li>• control of conception</li> </ul> and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means
2007	Directive 2007/47/EC	Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:  <ul style="list-style-type: none"> <li>• diagnosis, prevention, monitoring, treatment, or alleviation of disease</li> <li>• diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap</li> <li>• investigation, replacement or modification of the anatomy or of a physiological process</li> <li>• control of conception</li> </ul> and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means

disease in human beings or animals, or to make a medical diagnosis or to restore, correct or modify physiological functions. Note that reference is made only to the presentation and purpose of the medicinal product, without specifying its mechanism of action.

In Directive 2001/83/EC [3], the definition of medicinal product remains substantially the same, since it is modified only to exclude therapeutic use in animals; there is as yet no specification regarding the mechanism of action of the medicinal product.

In the premise of Directive 2004/27/EC [5], there is a mention concerning the need for a new and more specific definition of medicinal product, to account for the emergence of new therapies and also to take into consideration the growing number of so-called 'borderline' products that bridge between the medicinal product and other products, for example, medical devices. Clarifying the definitions seems necessary to avoid overlapping. Premise to directive 2004/27/EC states the need to improve consistency of the terminology of pharmaceutical legislation

introducing, within the definition of medicinal product, the specification regarding its type of action. So, the new definition of medicinal product, in 2004, specifies that a medicinal product shall influence physiological functions 'by exerting a pharmacological, immunological or metabolic action ...' [5].

A medicinal substance is thus a substance characterized as such not only on the basis of its therapeutic purpose but also in view of its capacity to modify physiological functions through a specific mechanism of action, which may be pharmacological, immunological, or metabolic.

## 2.2. Definition of medical device

The definition of medical device, first reported in Directive 93/42/EEC [6], has undergone fewer modifications than the definition of medicinal product. The earliest definition already delimited the purpose of medical devices on the basis of the mechanism of

action, stating that a device: ‘... does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means’.

### 2.3. Comparison of the definitions of medical device and medicinal product

From a reading of the definitions of medical device and medicinal product, it is quite clear that they overlap to some degree: medical devices and medicinal products are used in man or are administered to man for therapeutic or diagnostic purposes; in both cases, they may be substances/materials that are used in the treatment or prevention of diseases or in the restoration of physiological functions presumed to be altered.

From the first application of the medical devices directive, the CE certifications were requested for types of products that could be considered medical devices for ‘historical’ reasons (such as ‘surgical devices’, for example, syringes, I.V. drip chambers, dialyzers, catheters). Later the applications for CE certification started to involve products made of ‘substances’ which, due to their presentation, resemble medicinal products. Examples are products for topical use such as creams, gels, or ophthalmic solutions, nasal sprays, and aerosol therapy solutions, oral administration products, as well as intra-articular injection products, such as hyaluronic acid or other material. Due to their appearance and to cultural reasons, certain products are considered that they should be medicinal products more than others, independently of any scientific reason, while others are being accepted as medical devices, due to a starting acquaintance. Therefore, wound protection gels are well accepted as medical devices, while the same substance (e.g. sucral-fate) used to protect gastric ulcers (which are as much wounds as dermal wounds) are not. Some substances, such as simethicone, are being accepted as a medical device although it has been developed as a medicinal product, because of the 30-year gap from the medicinal and the device directives. Eye drops are being recognized as medical devices, while ingested products or products for vaginal or rectal application are finding more diffidence. History should remind us, however, that at the time when medicinal products were the only to be regulated, the regulatory requirements were much less than the requirements for a medical device. Good clinical practice, good manufacturing practices, good laboratory practices, and an objective preclinical and clinical development became routine later than any of the main current medicinal products were developed, and were developed at the same time as the device essential requirements.

## 3. Elements of demarcation between medical device and medicinal product

### 3.1. Mechanism by which a product exerts its principal intended action: the concepts of mechanism of action and effect

From a careful reading of the definitions of medical device and medicinal product, the main criterion to establish the applicable legislation is the definition and identification of

the mechanism by which the product exerts its therapeutic effect.

In the case of a medicinal product, the effect is achieved by a pharmacological, immunological, or metabolic mechanism of action, whereas in the case of a medical device the effective mechanism of action must not be Ph.I.M., although a Ph.I.M. mechanism may assist the device in its function.

Ambiguity arises first from the lack of a defined demarcation between a mechanism of action and the connected reaction by the human body and also from the lack of an analysis of the essential characteristics of the pharmacological, immunological, or metabolic mechanisms of action. Avoiding confusion between what is a ‘mechanism of action’ and what is an ‘effect’ is necessary to assess the mechanism of action of a substance, since the body always responds with pharmacological, immunological, or metabolic means, even to stimuli, which are non-pharmacological.

We must point out that ‘principal intended action’ is in fact the ‘claimed therapeutic effect’, therefore, the word ‘action’ is used with a meaning of ‘effect’.

### 3.2. The opinion of the European Parliament and the council

The above considerations highlight the importance to clarify these concepts, so that any procedure to decide on whether or not a product falls under the medical device definition, as indicated at point 13 of the ‘whereas’ section of Directive 2007/47/EC [7], be based on sound scientific grounds. It is important to know that there is also a need to analyze whether an action is a ‘principal intended action’ or an ‘ancillary action’ only when some performance of the device linked to its intended use is achieved with pharmacological means. Having a pharmacological ancillary mode of action within the device solely regards classification rules (specifically Rule 13), and further discussion of this aspect goes beyond the scope of this article.

The aim of this article is to analyze and propose to the legislator a series of definitions of fundamental terms needed to correctly assess whether a substance is a medicinal product or a medical device.

## 4. Terms and concepts

The first term to be looked at is that of ‘substance’ or ‘matter’ or ‘material’, considered equivalent terms in all discussions concerning medical device or medicinal product issues in this article. The definition given in Directive 2001/83/EC is clear and has been adopted.

The terms and concepts identified as fundamental to establish whether a product will be a medical device or a medicinal product are the following.

- (1) *Basic definition of mechanism of action and therapeutic effect*
- (2) *Definitions relevant to the different modes of action and to the identification of the principal intended action*

#### 4.1. Mechanism of action and therapeutic effect

The need to define the term ‘mechanism of action’ arises from the fact that a substance having a therapeutic effect is a medicinal product or a medical device depending on its mechanism of action.

We find it necessary to draw close attention to and define the concept of ‘mechanism of action’ because it still comes instinctive to confuse between the mechanism of action of a substance and its effect. Being unclear about this first concept creates a bias in the evaluation of all subsequent reasoning and data. Since the difference between medical devices and medicinal products is based on the mechanism of action, and also on the relationship between such mechanism and the intended effect of the product, it is of fundamental importance that the concept of mechanism of action be very clear.

In this sense, it is necessary to correctly interpret the first part of the definition of medicinal product, which needs to be linked to the mechanism of action.

The mechanism of action of a substance is defined in dictionaries and textbooks as the mechanism by which an active substance produces an effect on a living organism or in a biochemical system. The mechanism of action is usually considered to include an identification of the specific molecular targets to which a pharmacologically active substance binds or whose biochemical action it influences; a general recognition of the broad biochemical pathways (such as DNA synthesis, protein synthesis, metabolic pathways), which are affected (inhibited or promoted) by a substance is termed its ‘mode of action’ [8,9]. The concept of ‘mode of drug action’ is important to distinguish between actions of medicinal products and their effects. Actions of medicinal products are the biochemical physiological mechanisms by which the substance produces a response in living organisms. The effect is the observable consequence of the action of the substance.

As an example we know that to regulate heart rhythm, we may use digoxin (medicinal product), which binds to cardiac targets and increases the force of contraction of the myocardium. Or, we may install a pacemaker (medical device), which electrically stimulates the heart to contract. Again, to inhibit an inflammatory reaction, we may use an anti-inflammatory medicinal product that inhibits the synthesis and/or the action on receptors of the inflammatory mediators (e.g. NSAIDs), or we may use a material that traps the inflammatory agent (microbiological, chemical, or biochemical) and favors its removal without directly involving any receptor (e.g. a protective film).

In both examples, the effect is the same (therapy to the disease), but the intrinsic mechanism of action of the two products is different. In other words, the *effect* of the interaction between either product and the body is the same, but the *nature (the mechanism of action)* of the interaction is different.

For the purposes of this document, ‘pathology’ or ‘disease’ is understood as the set of signs and/or symptoms of altered physiological functions; therefore, by extension, ‘treatment’ or ‘therapy’ is understood as measures that exert a positive influence on these signs and/or symptoms to restore a normal physiological state. Therapy is on these terms the means of restoring the altered function, or the study and concrete application of measures and

methods for contrasting disease. The purpose of treatment or therapy, therefore, is to restore a pathological state to a healthy state, or to relieve symptoms to increase patient comfort.

The European Court of Justice has ruled in several cases in which a competent authority attributed a therapeutic effect to products/raw materials while the producer companies attributed only a physiological effect to their products. In this regard, the Court has ruled that a therapeutic effect is an *appreciable modification of physiological functions* (European Communities, Court of Justice, 2009) [10–12], where ‘appreciable modification’ is understood as a change that can be considered such as to shift the function in question from a pathological condition (which may be measurable with appropriate parameters) to a normal condition.

The meaningfulness of the effect of a substance/material on a living organism depends on the initial condition, on the nature and the dosage of the substance/material applied/administered, and on the principal intended action (intended purpose) of the substance/material, and must be evaluated case by case.

Examples of appreciable modifications, and therefore of therapeutic effects, include:

- a vaccine that induces an immune reaction against the inactivated microorganism administered by injection; the measurable parameter is the presence of antibodies specific for the microorganism in question.
- an imbalance among the mechanisms that regulate arterial blood pressure brought back into balance by one or more antihypertensive medicinal products; the measurable parameter is arterial blood pressure.
- hydration of the skin in cases of skin diseases, such as atopic dermatitis; the measurable parameter is trans-epidermal water loss and skin irritation.
- a substance that does not allow formation of biofilm of bacteria on surfaces by inhibiting adhesion; the measurable parameter is evidence of microbiological colonization.
- It is relevant that in the examples indicated the ‘mechanism of action’ and the ‘therapeutic effect’ are clearly different concepts. All examples report therapeutic effects, but the first two are achieved through a pharmacological mode of action, the second two through a non pharmacological one.

#### 4.2. Definitions relevant to the different modes of action and to the identification of the principal intended action

##### 4.2.1. The EU interpretation of the pharmacological, immunological, metabolic mechanism

The purpose of these definitions is to identify the characteristics common to the mechanisms of action proper to medicinal products (Ph.I.M), in order to clarify any ambiguities with respect to non-Ph.I.M. mechanisms of action, partly in consideration of the fact that MEDDEV 2.1/3 rev. 3 [13] provides definitions of these terms, which, for now, are not legally binding although they are the starting point for any proposal to legislators on these terms.



It must be noted that Directive 93/42/EEC [6] concerning medical devices speaks of material ‘which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means’, while Directive 2004/27/EC [5] relating to medicinal products speaks of substances administered ‘with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action’.

A specific definition of the terms ‘pharmacological’, ‘immunological’, and ‘metabolic’ as adjectives to ‘mechanism of action’ is, therefore, required for establishing a line of demarcation between medicinal products and medical devices. It is important to specify that ‘means’, ‘mechanism of action’, and ‘mode of action’ are synonyms.

The term pharmacology, as of today, in most text books describes both the mechanism of action and the effect of substances (medicinal products) on living organisms [8,9]. So defined it is an expansive science encompassing areas of interest relevant to many other disciplines. From a regulatory point of view, this creates confusion since Directives 93/42/EEC, the forthcoming recast regulation and Directive 2001/83/EC specifically require the characterization of the mechanism of action (and not the result) of devices and medicinal products.

Therefore, an analysis and definition of the terms pharmacological, immunological, and metabolic is important, conjugating the term pharmacology with respect to the mode of action, as stated in the relevant regulatory documents regarding devices and medicinal products.

The state of the art is that we find some definitions of pharmacological immunological and metabolic means in European guidelines (MEDDEVs).

From MEDDEV 2.1/3 rev. 3 [13]: ‘Pharmacological means’ is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect.

If the interaction of a substance is with a biological component (considered a receptor) and leads to direct and specific modifications of a biological pathway (signal) related to a physiological response, the mechanism of action of the substance is considered to be pharmacological.

Two further distinctions may be made within the compass of the pharmacological mechanism of action; these are:

- in the case that the interaction leads to direct and specific modifications of the immune system, the mechanism of action is considered to be immunological.
- in the case that the interaction leads to direct and specific modifications in basal cell metabolism, the mechanism of action is considered to be metabolic.

Thus, the definitions of immunological and metabolic mechanism of action derive mostly from what has been said above regarding the pharmacological mechanism of action.

MEDDEV 2.1/3 rev. 3 [13] describes immunological mechanisms as ‘... an action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific

immune reaction’. In this case, the word ‘specific’ does not refer to the specific (acquired or adaptive) immune response but rather to a ‘given’ immunological reaction.

For the definition of metabolic mechanism of action, we rely on the general definitions of a metabolic process, which includes all processes that produce energy for vital pathways, anabolic, and catabolic reactions where substances are handled by enzymes in the body with the purpose of assimilation and incorporation or detoxification and excretion. In MEDDEV 2.1/3 rev. 3 [13], the metabolic mechanism of a substance is defined as ‘... an action, which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function.

The fact that a product is, or is not, itself metabolized does not imply that it achieves, or does not achieve, its principal intended action by metabolic means. At the same time, a substance which is metabolized does not mean that it achieves its intended action by pharmacological means. In other words, the kinetics of a substance are not connected to its mechanism of action, while they may influence bioavailability at the active site.

#### 4.2.2. Chemical and physical modes of action

A chemical interaction is characterized by links among atoms (whether covalent, ionic, hydrophobic, electrostatic forces), which give different molecules than the starting ones.

A pharmacological mode of action necessarily entails a chemical interaction between the substance and a body constituent, however, not all chemical interactions yield pharmacological modes of action. As said above, a chemical interaction, which is not specifically linked to either activating or blocking a molecular signaling cascade is not involved in pharmacological processes.

Thus, actions mediated by acid-base reactions, solubility due to precipitation–complexation reactions, diffusion, redox reactions, which are not directly linked to the transduction of a signal are not pharmacological modes of action.

Physical modes of action involve the change in environmental conditions (thickness, porosity, flexibility, solubility due to temperature, osmolarity, surface tension, viscosity, mechanical resistance, polarity, shear resistance ...) through interactions, which do not yield new entities. They also, if not directly connected to a signaling cascade, are not pharmacological modes of action.

No definition is given on any official document for a chemical or physical mode of action.

Chemical mechanisms of action, which are not derived from a targeted interaction with a receptor and its signaling and physical mechanisms of action should fall into the category of non-Ph.I.M. mechanisms, and may therefore be proper to medical devices (Tables 2 and 3). A definition of both is proposed further in the article.

A mechanism, which entails the chemical interaction between substances in order to produce a change in the physical characteristics of the environment is a chemo–physical mode of action. We acknowledge that often the physical mode of action, which includes a barrier, is referred to as a mechanical mode of action.

**Table 2.** Examples of pharmacological, immunological, or metabolic mechanism of action.

Pharmacological mechanisms of action	
(a)	Interaction with an ionophore receptor: for example, the receptors for many neurotransmitters, such as the cholinergic system's nicotinic acetylcholine receptors, the GABAA receptor for $\gamma$ -aminobutyric acid (GABA), and several subtypes of glutamate receptors. Examples outside of the field of neurotransmission include glibenclamide, which interacts with and inhibits a $K^+$ channel in the pancreatic beta cells, causing a consequent secondary increase of intracellular calcium and increased insulin secretion
(b)	Interaction with the G-protein-coupled receptors, which are signal transducers for sending information from the receptor to one or more effector proteins (acetylcholine, catecholamines, eicosanoids, and opioids)
(c)	Interaction with receptors associated with enzymatic activities, such as the insulin receptor, a protein kinase that phosphorylates effector proteins present on the inner surface of the plasma membrane to start a cascade of reactions that translate into the metabolic effects proper to insulin
(d)	Interaction with an intracellular receptor; for example, the receptors for the steroid hormones, thyroid hormones, vitamin D, and retinol are soluble proteins that bind DNA and that lead to regulation of transcription of specific genes
(e)	Allosteric modulators which directly interact with the receptor as agonists or antagonists to influence receptor conformation. A typical example of allosteric agonists are benzodiazepines
Immunological mechanism of action	
(a)	Immunological medicinal products such as vaccines, toxins, sera, and allergens
(b)	Immunoglobulins
(c)	Monoclonal antibodies
Metabolic mechanism of action	
(a)	Substances that specifically inhibit enzymes regulating cell growth, renewal, and maintenance, such as statins, which inhibit hydroxymethylglutaryl-CoA reductase, an enzyme that regulates cholesterol synthesis
(b)	Enzymes used in enzyme replacement therapy for treating lysosomal diseases

**Table 3.** Examples of chemical and physical mechanisms and relative effects.

General chemical/physical mechanism of action	Specific chemical/physical mechanism of action	Effect in man
Capture/adsorption/inactivation/elimination/accumulation ...	Of the $H^+$ ion	Antacid effect
	Of free radicals (superoxidants, other types of radicals), called antioxidant	Antioxidant effect, generally, attenuating the effect of free radicals as trigger of inflammatory or allergic reactions
	Of water in the intestine	Laxative effect
	Of gases	Antigas effect
	Of nutrients/enzymes	Adjuvant effect in nutritional health
Filmogenic barrier effect (physical barrier)	Limits contact between tissue (skin or mucosae) and external or internal irritating agents	Protective effect against inflammatory agents
	Limits contact between tissue (skin or mucosae) and external or internal pathogenic agents (antiadhesion) Modifies the growth environment for microorganisms	Limitation of microbial contamination
Lubrication	Limits friction among internal or external elements	Lubricating effect
Chemical–physical action such as osmotic and tensioactive actions	Passive movement of bodily fluids across tissues, with different effects according to site of action Induces change of viscosity	Mucoregulatory effect
		Hydrating effect Laxative effect
Osmotic action	Induction of a change of viscosity Hindrance of biofilm formation Transient reduction of mucosal/skin barriers	Mucoregulatory effect Limitation of microbial contamination Permeation enhancer

#### 4.2.3. Mechanism of action toward pathogens

The mechanism of action toward pathogens is a good example to distinguish between a pharmacological and a chemical/physical mode of action.

In some cases, the medical device has intended purposes that include the interference with the activity of a pathogen on or within the human body. It is clear that the activity of a substance that specifically interferes with biochemical pathways of the microorganism so that its replication and/or viability are impaired constitutes a pharmacological mechanism as carried out by antibiotics of all types. On the other hand, changing the environmental conditions (osmolarity, pH, surfactants, chelators, shields of the adhering surfaces) constitutes a physical or

chemico–physical mechanism of action. An example of such action is that of cranberry extracts whose mechanism is related to interference with surface adhesion molecules of the bacteria inducing conformational changes and, therefore, not allowing the formation and development of a proper biofilm and resulting (therapeutic effect) in reduced colonization by the bacteria [14,15].

#### 4.3. Summary and examples

Some examples of pharmacological, immunological, or metabolic mechanism of action are indicated in Table 2.

**Table 4.** Examples of effect and corresponding Ph.I.M. and non-Ph.I.M. mechanism of action.

Effect in man	Ph.I.M. mechanism of action	Non-Ph.I.M. mechanism of action
Antacid	Antagonist of the H <sub>2</sub> histamine receptor (ranitidine) Inhibition of the Na <sup>+</sup> /H <sup>+</sup> ATPase pump (omeprazole)	<i>Chemical mode of action</i> Neutralization of the H <sup>+</sup> ion (acid–base action)
Anti-inflammatory	Inhibition of cyclooxygenase (NSAIDS) Inhibition of proinflammatory gene expression (glucocorticoids)	<i>Chemical mode of action</i> Chemical reactions with noxious agents (scavenging of free radicals, chelation of pro-oxidant metals, complexation /denaturation of proinflammatory proteins) <i>Physical mode of action</i> Formation of a protective barrier to limit contact between tissue and external or internal irritating agents
Laxative effect	Pharmacologically induced water movement toward the lumen of the intestine (Lubiprostone)	Passive water movement toward the lumen and retention of fluids in the intestine (glycerol, mannitol, other osmotic agents ...)
Increase of excretion of dietary fats	Specific inhibition of lipase	Capture of lipids in the intestine
Barrier effect	Not applicable <i>Preventing contact by means of a barrier effect is not a Ph.I.M. mechanism of action</i>	Limitation of contact between tissue (skin or mucosae) and irritating agents (mechanical shields, substances, which adhere and cover skin or mucosae ...)
Lubricating effect	Not applicable <i>Limiting friction is not a Ph.I.M. mechanism of action</i>	Reduction of friction among internal or external elements
Limitation of microbial contamination	Specific interference with microbial metabolism/ reproduction (antibiotics)	Limitation of contact between tissue (skin or mucosae) and other surfaces and external or internal pathogenic agents Modification of the microenvironment

To summarize what has been discussed above and give examples of both Ph.I.M and non-Ph.I.M modes of action and to review the distinction between mode of action and therapeutic effect, [Tables 3](#) and [4](#) are presented.

## 5. Proposed definitions

The information presented above suggests that in fact pharmacological means underlies all the Ph.I.M. mechanisms of action. In other words, the immunological and metabolic modes of action are specific pharmacological actions. The Ph.I.M mode of action describes the fact that the interaction between substance and organism is such, in terms of site of action (receptor or receptor-like elements) that specific reactions are triggered within the cell as a direct result of the interaction between body and substance. In this case, the biological response is the therapeutic effect.

Receptors designated to bind with endogenous substances are at the start of chains of interactions (signal transduction) that constitute common reactions to different stimuli. An external substance acting on a given receptor via a pharmacological mechanism of action must necessarily mimic or oppose the action of the relative endogenous substance. For this reason, a substance acting by pharmacological means will modify the existing biochemical pathway linked to its receptor. This includes allosteric modulators, which interact specifically with the receptor and directly influence the receptor and the signal transduction.

The immunological mechanism of action is a type of pharmacological mechanism of action, in that the immunologically acting substance binds to an endogenous element (receptor) of the immune system and triggers a specific reaction in the body.

The above must also be considered in relation to metabolic mechanisms of action; that is, we must take into account that metabolism is the sum of the catabolic and anabolic reactions that take place in a cell, tissue, or organ. Metabolic pathways

are, thus, orderly sequences of chemical reactions that benefit from the catalyzing activity of many proteins, the enzymes, which besides favoring and speeding up a reaction create a 'one-way street' for the reaction, either toward breakdown or buildup.

The chemical mechanisms of action involve transformation of the very nature of materials (for example, acid–base reactions). They differ from pharmacological means by the absence of interaction between the substance and a receptor. It is true that 'old school' pharmacology has considered direct chemical or physical interactions to be 'pharmacological actions not mediated by receptors' [16], such as osmotic laxatives, chelators, and antacids. Currently, substances acting by these means are regulated as medicinal products solely in virtue of their historical use and formal aspect, in accordance with the definition of medicinal product in force prior to 2004. In truth, these substances do not produce their effects by interacting with a receptive tissue component but with small molecules or ions in extracellular regions or by modifying only the chemical–physical or biological conditions of such a region.

Overall, we propose to the legislators the following general paradigm (see also [Table 5](#)).

According to the issues analyzed above, definitions in medical device regulation directed to define any pharmacological, immunological, metabolic mode of action should:

- (1) mention of a targeted and specific interaction with a cellular constituent directly and specifically linked to chemical signaling pathways between and within cells (specificity of the interaction),
- (2) mention that such modification brings about significant changes to the connected biological pathway (transduction of the signal) (it is important not to confuse biological pathway with physiological/pathological function, which would be the effect!),



Table 5. Summary of the definitions proposed.

Main concept	Current definition	Proposed definition
Pharmacological	'Pharmacological means' is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect	'Pharmacological means' is understood as a TARGETED interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect
Immunological	'Immunological means' is understood as an action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific immune reaction	'Immunological means' is understood as a TARGETED action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific immune reaction
Metabolic	'Metabolic means' is understood as an action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function	'Metabolic means' is understood as a TARGETED action, which involves an alteration, including stopping, starting or changing the speed of the chemical processes participating in AND MODULATING THE USE OF ENDOGENOUS OR EXOGENOUS SUBSTANCES FOR THE GENERATION OR STORAGE OF ENERGY AND ANY CATABOLIC OR ANABOLIC PROCESS IN THE BODY
Chemical	–	Chemical mechanism of action is intended as the interaction of a substance with other substances present in the body, such as to transform the initial chemical substances (the reactants) into different chemical compounds (the reaction products). These actions should not include the targeted interaction with a receptor and its signaling pathway
Physical	–	Physical mechanism of action is intended as the interaction of a substance/material with other substances present in the body, such as solely to transform the surrounding environment/matter
Relevant	–	Relevant action of a medical device: an effect induced in the body by a substance/material, which contributes to the stated therapeutic effect according to the indications (intended purpose) of the product
	–	Relevant mechanism of action of a medical device: the mechanism of action responsible for the relevant action of the product
Principal	–	Principal action of a product: the effect of the product on the body that is necessary and sufficient for achieving the claimed therapeutic effect
	–	Principal mechanism of action of a product: the mechanism of action responsible for the principal action of the product
Ancillary	–	Ancillary action of a medical device: the effect of the product on the body that completes (assists) the principal action to optimize performance, but is not necessary for achieving the claimed performance
	–	Ancillary mechanism of action of a product: the mechanism of action responsible for the ancillary action of the product

- (3) avoid reference to the concept of 'indirect' since it would lead to confusion between mechanism of action and therapeutic effect,
- (4) avoid reference to the entity of the result on the physiological or pathological function since it may create confusion between mechanism of action and therapeutic effect. This aspect is defined elsewhere in the definition of both the medical device and the medicinal product,
- (5) avoid excessive list of examples within the definition since it may be confusing.

Although it is true that the only definition of pharmacological, immunological and metabolic mode of action is reported in MEDDEV 2.1/3 rev. 3, and that there is certainly always room for improvement, let us evaluate these definitions in light of the above stated points to consider.

### 5.1. Definitions of the Ph.I.M. modes of action

- (1) Pharmacological mode of action (MEDDEV 2.1/3 rev. 3):

*'Pharmacological means' is understood as an interaction between the molecules of the substance in question and a*

*cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect.*

This definition does not have any confounding elements. The elements of specificity between the substance and the target are implied, with the word 'receptor' although not explicit. The influence on the transduction of the signal is contained in the word 'response'. The word response should be interpreted in the sense of 'cellular response' and not in the sense of therapeutic effect. It is implicit also that the definition is the same independently from the type of organism where it is explicit: man, animal, microorganism.

For the sake of clarity the definition should be interpreted by making more explicit the concept of specificity, as follows:

*'Pharmacological means' is understood as a TARGETED interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect.*

It may be useful to cite here a working definition of receptor: 'a cellular macromolecule, or an assembly of macromolecules, that is concerned directly and specifically in a chemical signaling between and within cells. Combination of a hormone, neurotransmitter, medicinal product, or intracellular messenger with its receptor(s) initiates a change in cell function' [8].

(2) Immunological mode of action (MEDDEV 2.1/3 rev. 3):

*'Immunological means' is understood as an action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific immune reaction.*

This definition does not have any confounding elements, the concept of specificity could be strengthened, and interpretation of the definition should be as follows:

*'Immunological means' is understood as a TARGETED action in or on the body by stimulation and/or mobilization of cells and/or products involved in a specific immune reaction.*

(3) Metabolic mode of action (MEDDEV 2.1/3 rev. 3):

*'Metabolic means' is understood as an action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function.*

*Note: The fact that a product is, or is not, itself metabolized does not imply that it achieves, or does not achieve, its principal intended action by metabolic means.*

There are no confounding elements although the definition may be a bit too general, especially regarding the 'normal body function'. The concept of specificity and of direct intention is lacking. Here, the concept of 'normal body function' could be better defined with the words: *'Metabolic is any activity modulating the use of endogenous or exogenous substances for the generation or storage of energy and any catabolic or anabolic process in the body'.*

A possible proposal for interpretation of the definition, which includes the concept of specificity could be:

*'Metabolic means' is understood as a TARGETED action which involves an alteration, including stopping, starting or changing the speed of the chemical processes participating in AND MODULATING THE USE OF ENDOGENOUS OR EXOGENOUS SUBSTANCES FOR THE GENERATION OR STORAGE OF ENERGY AND ANY CATABOLIC OR ANABOLIC PROCESS IN THE BODY.*

## 5.2. Definitions of the non- Ph.I.M. modes of action

The two main non-Ph.I.M. modes of action, which we envisage are the chemical and the physical modes of action (see Table 5).

As regards the chemical and physical modes of action, no definitions are found, and we therefore propose starting point definitions, as follows, keeping in mind the general paradigm reported above:

(1) Chemical mode of action

*Chemical mechanism of action is intended as the interaction of a substance with other substances present in the body, such as to transform the initial chemical substances (the reactants) into different chemical compounds (the reaction products). These actions should not include the targeted interaction with a receptor and its signaling pathway.*

(2) Physical mode of action

*Physical mechanism of action is intended as the interaction of a substance/material with other substances present in the body, such as solely to transform the surrounding environment/matter.*

## 5.3. Mechanism by which a product exerts its principal intended action: the concepts of principal intended action and ancillary action

Having seen the difference between mechanism of action and effect, and having analyzed the Ph.I.M. mechanisms of action, for the sake of completeness with respect to the definition of medical device, another issue that needs to be looked at is the concept of 'principal intended action' since, according to its definition, a medical device 'does not achieve its principal intended action ... by pharmacological, immunological or metabolic means, but ... may be assisted in its function by such means'.

The principal intended action is the action responsible for the performance characteristics of a product, according to its intended purpose. From the discussion in the previous paragraphs the 'principal intended action' is understood as the 'effect' or 'therapeutic effect' that the device is intended for. In fact, a mechanism of action that does not induce the intended therapeutic effect must be considered as not relevant to the product's intended purpose, being obviously relevant for safety assessment.

Substance based medical devices may have more than one action concurring to the claimed therapeutic effect: i.e. lubrication and osmotic action, or chelation and acid base reactions, or adhesion and redox actions. All those which are necessary for the achievement of the claimed performance of the product are actions which concur to the 'principal intended action' and therefore relevant to the analysis of the principal mode of action.

The following considerations can be given to identify an action which constitutes the principal intended action:

- (1) The action must be relevant, that is, it must contribute to the intended performance of the product according to its intended use.
- (2) It must be necessary in order to achieve the claimed performance.

In their entirety, all actions necessary to achieve the intended use of the device constitute the 'principal intended action', which needs to be non Ph.I.M.

We then propose to the legislators the following definitions:

*Relevant action of a medical device: an effect induced in the body by a substance/material, which contributes to the stated therapeutic effect according to the indications (intended purpose) of the product.*

*Relevant mechanism of action of a medical device: the mechanism of action responsible for the relevant action of the product.*

*Principal action of a product: the effect of the product on the body that is necessary and sufficient for achieving the claimed therapeutic effect.*

*Principal mechanism of action of a product: the mechanism of action responsible for the principal action of the product.*

*Ancillary action of a medical device: the effect of the product on the body that completes (assists) the principal action to optimize performance, but is not necessary for achieving the claimed performance.*

*Ancillary mechanism of action of a product: the mechanism of action responsible for the ancillary action of the product.*

## 6. Expert commentary

The medical device definition is very broad and includes a wide variety of products, among which substance-based medical devices require specific attention. The definition of medical device and that of medicinal product introduce the concept of mechanism of action, and the terms pharmacological, immunological, and metabolic, which now acquire regulatory importance. This does not allow for any misleading nor ambiguous interpretation of these terms, since jobs and innovation and health of the European people are at stake.

The medical device directive, and forthcoming recast regulation, accept the presence within the device of an added substance with a pharmacological mode of action, provided that this action is not responsible for the intended use of the device but may, for example, ease the use of the device by the user/patient, with consequent reduction of possible discomfort deriving from application/use (e.g. urinary catheters lubricated with lidocaine). We felt that regulatory documents often are not unequivocal in the interpretation of key terms, such as 'action' of a medical device compared to the 'mechanism of action' of such device. And within the 'mechanism of action' there is still some controversial interpretation as to the pharmacological (immunological or metabolic) or non pharmacological action of a substance. In any decisional procedure, the correct interpretation of these and other correlated terms is needed to correctly assess whether a substance is a medicinal product or a medical device. In this article, we have proposed definitions of essential terms and a paradigm for any further development. Specifically we have analyzed the difference between the concept of 'action' and 'mechanism of action' of a product and defined other important correlated terms, knowing that their correct interpretation is crucial for an accurate assessment of whether a substance-based product is a medical device or a medicinal product.

## 7. Five-year view

The increasing presence of substance-based medical devices has brought the forthcoming recast regulation to recognize

and directly address them through a specific classification rule and evaluation methods. Since substance-based medical devices and medicinal products may look alike and differ only by their mechanism of action, it will be always more important to have a clear and homogenous interpretation of the essential terms at the base of regulatory assessment of substance-based products. A sudden rush to define the scientific terms, such as those presented in this article without the necessary time and specialized personnel is envisaged and needs to be avoided, since ambiguous and misleading definitions would endanger innovation and patient health. We prospect and hope that the definitions provided here, as well as the paradigm for any future development of the definitions shall be a useful tool for a correct assessment of substance-based products in the future. We prospect that such assessment shall be an increasingly essential and frequent challenge for manufacturers, notified bodies, and Competent Authorities, as well as scientific reference personnel.

## Key issues

- Development of medical devices depends heavily on clear regulations and these affect the performance of the innovation for patient health.
- The term medical device includes a wide variety of products, yet some of them, such as substance based medical devices are particularly sensitive to ambiguity in regulatory definitions.
- According to definitions regulating the classification of a product within the category of medical devices or medicinal products, particularly important are the concepts of mechanism of action and therapeutic effect, as well as of pharmacological, immunological, metabolic, and NON-pharmacological, immunological and metabolic mechanisms of action.
- Lack of a correct interpretation and definition of these terms would impact on the effective development of the products.
- A correct interpretation and definition of the terms which are at the base of regulatory issues would bring overall benefit to innovation and health management.

## Funding

This paper was partially funded by an unrestricted educational grant from Aboca S.p.A.

## Declaration of interest

M Racchi has received support of research from the Crowdfunding Initiative University of Pavia. L Capone is employed in the regulatory/research division of Aboca S.p.A and participated in literature research, scientific discussion, writing and proofreading of the text. E Giovagnoni is employed in the regulatory/research division of Aboca S.p.A and participated in order to supply scientific and regulatory support. Contributed to the original idea and final discussion of the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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