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The concept of non-pharmacological mechanism of action in medical devices made of substances in practice: what pharmacology can do to promote the scientific implementation of the European medical device regulation

M. Racchi, Govoni S.

Department of Drug Sciences, University of Pavia, Pavia, Italy

E-mail: racchi@unipv.it

Summary
Medical devices represent a wide category of products intended to be used in the prevention, diagnosis, monitoring, treatment or alleviation of a disease or injury and their most recent evolution has led to an increasing number of products that include "substances" and which, due to their presentation and site of application are similar to medicinal products and are often referred to as "borderline" products. Regulatory documents in the European Union (EU) contemplate substance based products in many regulatory areas; in therapeutics, they distinguish "medical devices" from "medicinal products" according to the principal mechanism of action of the product. This difference is often not intuitive and is based on the correct interpretation of essential terms as "pharmacological, immunological and metabolic mechanism of action", which have important regulatory implications. This paper addresses the issues concerning the correct interpretation of these terms and wishes to attract the interest of pharmacologists to design proper experimental paradigms to be applied to the rigorous and scientific interpretation of the correct mechanism of action of medical devices made of substances.

Introduction

Medical devices represent a wide category of products such as apparatus/instruments, software, and materials intended to be used in the prevention, diagnosis, monitoring, treatment or alleviation of a disease or injury. Today they play an increasingly important role in the healthcare system and the industrial sector connected has grown to significant numbers in terms of annual revenue (1). Unmet medical needs, including illnesses with a relative low grade of risk but shared by many patients and the increased incidence of chronic conditions and syndromes, highlight the need to continue evolution in the monitoring, diagnostic and therapeutic fields. These needs represent a significant opportunity to introduce innovative products, which could represent effective tools in the management of particular medical conditions, with beneficial outcomes for patients. Within this context, medical devices are a category of products which may allow to design innovative interventions since the medical device regulatory horizon is based on a general risk/benefit evaluation of a wide variety of products, which are considered on a case by case basis according to general requirement indications. The evolution of medical devices has led to an increasing number of products that include "substances" and which, due to their presentation (powders, liquids, tablets) and to their sites of application (i.e. gastrointestinal mucosae reached via oral administration), resemble those products which have historically been called medicinal products. A new regulatory document in the European Union (EU) has recognized and directly addressed them as “Devices that are composed of substances or of combinations of substances” (Regulation 2017/745) (2). Other wordings for these devices are “substance based medical devices”, or “medical devices made of substances” (MDMS). In particular, Regulation 2017/745, issued by the EU Parliament and the Council after in depth discussion of scientific and health related issues regarding patients, identifies a specific classification rule (Rule 21) for medical devices made of substances. This rule introduces medical devices made of substances which need to be absorbed in order to achieve their intended action. This is another important similarity with medicinal products that raises the need to better define the differences between the two categories, as to promote innovative interventions and not lose therapeutic opportunities. Where is the difference then between the two classes of products then? The difference between substance-based medical devices and medicinal products can be found in their mechanism of action, as per the definition of “medical device” and “medicinal product”. However, this difference is not intuitive, thus the importance of expert involvement. The key point then is the clear and homogenous interpretation of the essential terms at the base of regulatory assessment of substance based products. With this paper we would like to stimulate the discussion among pharmacologists and regulatory authorities on the possibilities to contribute to the development of new innovative products while defining the proper regulatory concepts.

Medical devices and medicinal products share the common essence of having a therapeutic effect, yet they are substantially different in the mechanism of action by which they achieve such effects.

The core of this paper is to discuss the definitions currently accepted in the EU legislation, discuss them in the light of state of the art pharmacology, and discuss the possibilities and urge for pharmacologists to clear some of the controversies when legislators and manufacturers have to discuss on the actual meaning of terms.

The paper presents and discuss the opportunity for pharmacologists to approach a complex definition problem both from a theoretical and an experimental point of view.

A brief history of regulatory definitions

In the history of regulation of medicinal products in Europe (Directive 65/65/EEC (3)), the earlier definition of “drug” in 1965 required only that the product be presented and claimed as having a therapeutic purpose (i.e., to act on altered physiological functions). From 1965 to 2004 the definition of medicinal product remains essentially the same.

Directive 65/65/EEC defined a medicinal product as having the “purpose of treating or preventing disease in human beings or animals, or make a medical diagnosis or to restore, correct or modify physiological functions”, it is to be noted 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 (4), 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.

It is only with Directive 2004/27/EC (5) that a more specific definition is presented of a medicinal product. In the premise if the directive 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 needs to be pharmacological, immunological, or metabolic. On the other hand, the definition of medical device, first reported in Directive 93/42/EEC (6) has undergone specifications but no modifications regarding the mechanism of action up to the most recent Regulation 2017/745/EC (2). 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". The most interesting novelty of Regulation 2017/745/EC, as anticipated in the introduction, is a more explicit acknowledgement of the importance and peculiarity of devices made of substances and the possibility of such products to exert their action following systemic administration and absorption (Rule 21 first indent) (2).

Terms and concepts

It may seem like a mere exercise of semantics however the correct use and interpretation of terms concerning a matter of health care products is of pivotal importance and should be expressly addressed by health care professionals. We have seen that the key terms used in the EU definition of a medical device are concerned with the "intended action" of the device, its "mechanism of action", the need to exclude a "pharmacological, immunological or metabolic (Ph.I.M) mechanism of action" and, according to Regulation 2017/745/EC with "medical devices made of substances" (MDMS).

We present here the state of the art regarding the main definitions which establish whether a product will be regulated as a medical device or a medicinal product. The interpretation of these terms would surely benefit from a clear discussion from the point of view of the pharmacologists in order to ensure scientific knowledge as well as methodologically sound approaches when experimental data is needed.

Mechanism of action vs therapeutic effect

One of the first ambiguities in the legislation is the correct interpretation and distinction between the "therapeutic effect" of the product and its "mechanism of action". It still comes sometimes instinctive for those not acquainted with pharmacology to confuse between the "mechanism of action" of a substance and its "effect". When taking into account a Pharmacology textbook we can read that the effect produced by a drug can be recognized as an alteration in a function/process that maintains the existence of the living organism. The effect is what is produced by the drug and is distinguished from the mechanism of action which relates to where (site of action) and how the effect is produced (7).

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.

Just to make a simple example we can consider that there are two means to promote evacuation for the treatment of constipation. We may use lubiprostone, a molecule which is well characterized as a ligand of type-2 chloride channel (ClC-2) in the gastrointestinal tract, increasing chloride concentration in colon fluid with associated passive transport of sodium across the mucosa, thus generating a water movement toward the lumen of the intestine, or glycerine, a molecule which directly, independently of an interaction with cellular components and based solely on its concentration in the applied solution, establishes a hyperosmotic environment at the site of action (8).The effect of both substances is to increase fluid into the colon lumen which promotes peristaltic waves and alleviates constipation, but the mechanism of action of the two substances is profoundly different. We see therefore that the "effect" and "mechanism of action" are clearly distinct. The only official definition of mechanism of action is found in FDA (9) and is defined as "(k) Mode of action is the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition", "therapeutic action or effect includes any effect or action of the product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body". For regulatory purposes, the terms "pathology" or "disease" represent a set of signs and/or symptoms of altered physiological functions. As a consequence and by extension, the terms "therapy" and "treatment" represent those actions and measures that positively modulate "pathology/disease" conditions to restore a normal physiological state. 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. MDMS may have more than one mechanism of action concurring to the claimed therapeutic effect: i.e. lubrication and osmotic mechanisms, or chelation and acid base reactions, or adhesion and redox mechanisms of action. Those mechanisms necessary to achieve the claimed performance of the product concur to the "principal intended action" and therefore must contribute to the intended performance of the product according to its intended use and must be necessary in order to achieve the claimed performance. In all this, they should not rely on a "pharmacological, immunological or metabolic" mechanism of action. Some more examples of therapeutic effects in man yielded by both pharmacological and non-pharmacological modes of action have been listed by Racchi et al. (10).

Pharmacological, immunological and metabolic mechanisms

The terms "pharmacological", "immunological" and "metabolic", resumed in the general acronym Ph.I.M. are adjectives to "mechanism of action" and are specifically required to establish the line of demarcation between medicinal products and medical devices. This is the crucial point to all classification issues regarding substance-based products. There is no internationally approved definition of Ph.I.M modes of action, but the terms are defined in Meddev 2. 1/3 rev 3 (11). Since the interpretation of this term has implications on the products which shall be regulated (or not) as medical devices, it seems that the involvement of both scientific and regulatory experts is necessary in order to allow the application of the Medical Device Regulation. Racchi et al (10) have analyzed these definitions and made some considerations reported in the table below (**table I**).

Table I. Pharmacological mode of action possible definitions.

Main concept	Current definition from Meddev 2. 1/3 rev 3	Comment for a more precise definition
Pharmacological mechanism of action	"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.

The definition from Meddev is clear and pinpoints two important elements of the pharmacological mode of action: the need for the molecules of the substance to act on a receptor and the need for a direct response (or a lack of a direct response) of the receptor as a result of the interaction with the molecule. Receptors are defined as “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” (13).

In other words, the pharmacological mode of action requires a molecule which acts on a receptor selected for the role it plays in the relevant physiological function. So, the starting point for achieving the therapeutic effect with a pharmacologically acting molecule is the selection of the target receptor and the control that the adequate molecule -receptor mechanisms take place.

Pharmacology textbooks refer to this as the key-lock model, which exemplifies the core of pharmacology (7). From a regulatory point of view, the molecule interacting with the receptor is the active pharmaceutical principle (API) of a medicinal product. Logically, Directive 2001/83/EC requires the determination and mechanistic description of the individual interaction between the API and its target receptor. For this reason, a clarification of the definition of pharmacological mechanism of action would be to specify that it entails a *targeted* interaction. Similar comments have been made on the immunological and metabolic definitions. Indeed, these concepts including the one referring to receptor and receptor-mediated actions have evolved to interpret the mode of action of modern biotechnological drugs. A siRNA or a monoclonal antibody are examples of very specific biological molecules interactions even if they do not fit the definition of drug/receptor interaction. It is true that the steps at the base of drug development are directed towards finding the intended target and selecting the best ligand according to the intended use (agonist or antagonist). Subsequently qualitative and quantitative determinations are made in order to best describe the interaction between the ligand and its specific target. As anticipated these concepts can be broadened to more modern interpretation of the pharmacological mechanism of action even if it does not include a classical ligand-receptor interaction, yet they maintain the features of a single targeted interaction.

Medical devices stand on a different mindset: although each component serves its role, the performance and the therapeutic effect is ascribed to the entire product, not to a specifically targeted interaction, and the fact that either each of the components or the entire complex do not have pharmacological, immunological, metabolic mechanism of action.

Medical devices made of substances and complex substances

As mentioned previously, medical devices made of substances and complex substances, often have more than one non-pharmacological mechanism of action concurring to the claimed therapeutic effect. This is due to the fact that different types of interaction between the medical device and the human body concur to the effect; they are the result of all of the features of the product, which are due to all its components. This is particularly clear with medical devices made of natural substances, which are regulated by legislations as different as food, dietary supplements and medicinal products. Natural substances have the specificity of being complex, i.e. composed of a very high number of molecules, acting in synchrony, in a way that is best represented by the concept of “system”. The “system” in fact is different than the sum of its components since it includes the inter-reactions and inter-relations among each molecule as well as the properties deriving from intermolecular interactions, such as chemical physical behavior, of the entire composition, which can only be observed when the system is integral. Given for granted the need for proper standardization, safety assessment and proper clinical evidence of efficacy, it is clear that it is necessary a different theoretical and practical approach.

The active system interacts with the cellular components in a way that cannot be individually determined, but it can be statistically modelled in order to generate a prediction of some of its features.

This process is only possible ex-post, through the observation of the effects that the system exerts on the organism and based on the features of interaction that certain components of the system are known to establish with cellular components when they are purified, therefore not in the chemical environment determined by the mixture. Medical devices made of substances and complex substances therefore require a different approach than pharmacologically active ingredients. The change in approach should lead to a change in regulatory attitude. Considering medicinal products, technically and practically, they are mostly composed of a single active pharmaceutical ingredient (API) that have one main target and modify body functions with mechanisms that mostly respond to the description of the "Ph.I.M." mechanism discussed above.

Complex natural substances, have interactions with multiple targets, interconnected and interrelated, but not individually identifiable and quantifiable as separate entities hierarchically organized.

There are increasing cases in which their therapeutic effect is well visible, but their mechanism of action cannot be described without approximations. This is possibly due to lack of sensitivity or appropriate methods however as we stand today two approaches can be followed. One approach is to identify and select one marker of the complex natural substance as the active principle and isolate it for a complete drug development. This allows to develop the product according to Directive 2001/83/EC but does not account for the cooperative action with other components of the complex mixture that may be instrumental to the final *effect* but not to the single molecule *mechanism of action.*

The other approximation is to consider a specific extract indicated by regulators, as the medicinal product. Since this consideration does not allow drug development according to Directive 2001/83/EC, an important derogation was made, with Directive 2004/24/EC, which introduced the registration of "traditional herbal medicines". This is a partial registration where safety is given by the long-standing use of the identified extract in the identified conditions of use, while the mechanism of action and the clinical efficacy of the product do not need to be demonstrated and are assumed as plausible, due to long standing use of the specific extract in the EU. To this regard, the European Medicines Agency (EMA) has published a set of Herbal Monographs for traditional medicinal product authorization, which indicate for a specific type of herbal extract (ie icelandic moss herbal tea or tincture), a plausible indication (pharyngeal protection for sore throat) but do not indicate the pharmacodynamics or pharmacokinetic features of that extract (14). Traditional medicinal products registrations de facto acknowledge the impossibility to describe the pharmacokinetics and pharmacodynamics of a complex substance, as required of a "medicinal product", precisely due to their complexity. This should not hamper the possibility to test on a clinical setting the potential therapeutic effect of the complex substance, still standing the fact that with appropriate methods and sensitivity, a specific mechanism of action could be described.

This potential should not be lost, but rather scientifically delved into, and main actors could be pharmacologists, clinicians and regulators. The lack of a valid adequate conceptual model describing the mechanism of action of natural complex substances risks to force them into traditional herbal medicine registration de facto not allowing innovation since the regulatory backbone of this registration is the long-standing use of the specific indicated extract.

Regulation 2017/745, by identifying medical devices made of substances and specifying that some has already indicated, from a regulatory point of view, that natural complex substances have the features of medical devices. These include having a therapeutic effect which is not reached with a pharmacological mechanism of action. Looking at the features of the pharmacological mode of action (key-lock model as broadly defined before), it seems evident that it does not fit the mechanism of action of complex natural substances.

In parallel, the deterministic methods used to describe the mechanism of action of single APIs cannot describe that of a "system".

The time has come to identify and discuss experimental models which allow to gather scientific information on these complex multiple target products in order to best describe their mechanism of action.

One suggestion is to use the tools of "systems biology" models, which allow to work backwards from the observed biological effects collected in order to propose possible triggers. These models could be the pre-clinical evidence needed to describe, albeit with the limitations previously described, the putative events underlying the efficacy and safety assessed during product development. However, the question remains, which kind of mechanism of action should this be? Since the main issue between a medicinal product and a medical device is the pharmacological mode of action, this spurs an in-depth analysis of what the pharmacological mechanism of action really is, at root, in order to identify adequate models to investigate for it, as well as to investigate how to best measure non-pharmacological modes of action.

Identifiable targeted interaction as intrinsic part of the pharmacological mechanism of action

According to Annex I of Directive 2001/83/EC, the registration of a medicinal product requires the detailed description of the active ingredient and of its interaction with its target receptor (pharmacodynamics). What kind of mechanism of action is there when a product interacts with the biological environment without an a priori targeted key-lock approach? De facto, it seems that a product which cannot be described according to a key-lock mechanism cannot comply with the medicinal product regulation (Annex I of Directive 2001/83/EC).
There are intuitive situations such as chemical/ physical mechanisms of action. These include acid-base, lubrication, barrier formation. However, it can be true of other types of interactions which cannot be described according to the key-lock model due to their complexity, such as products made of natural substances and combination of substances, which do not match the key-lock mechanism because the interaction of each molecule with its target receptor cannot be individually identifiable and measurable also because of the lack of proper methodology and sensitivity.
Therefore, their mechanism of action does not fit the pharmacological, immunological or metabolic classic paradigm with recognizable targeted specific interactions and may be classified as non-pharmacological in order to promote their proper assessment in clinical trials, as indicated by the new Medical Device Regulation (2).
The EU regulatory documents for either medicinal products or medical devices do not provide an explicit designation of the “non-pharmacological” (and by inference non-immunological or metabolic) mechanism of action, which, in practice, are identified in Europe, with the physical and chemical modes of action. However, these terms are also not officially defined. Racchi et al. proposed (10) a regulatory definition of chemical and physical modes of action. The 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 into different chemical compounds (the reaction products). These substances are not specifically targeted ligands to an individually determined receptor on which they may behave as agonists or antagonists (which is the pharmacological mode of action).
The physical mode 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. In Pharmacology often direct chemical or physical interactions have been considered to be “pharmacological actions not mediated by receptors” (15) and substances that act via such mechanisms are regulated as medicinal products mostly because of their historical use and formal aspect, in accordance with the definition of medicinal product in force prior to 2004, while in truth, they produce their effects with mechanisms that may be indicated as non Ph.I.M. according to the EU definitions. Physical modes of action that involve the change in environmental conditions (thickness, porosity, flexibility, solubility due to temperature, osmolarity, surface tension, viscosity, mechanical resistance, polarity, shear resistance …) should fall into the category of non-Ph.I.M. mechanisms, and should therefore be proper to medical devices. Experimental protocols showing the difference between a pharmacological mode of action and a physical mode of action (osmolarity) have been developed (8), and other models to show the non-pharmacological nature of other mechanisms are called for.
It is our opinion and suggestion that all reactions triggered by complex substances, where the trigger does not match the broadly defined targeted key-lock model, be considered from a regulatory point of view non-Ph.I.M. modes of action. This includes multiple reactions between complex substances and the human body which can be described only with a “systems biology” approach, intrinsically characterized by the degree of uncertainty conceptually deriving from the application of statistical modelling tools, to knowledge of the behavior

of a molecule when in a different chemical environment, as proposed above.

Systems biology has been defined as "a scientific approach that combines the principles of engineering, mathematics, physics, and computer science with extensive experimental data to develop a quantitative as well as a deep conceptual understanding of biological phenomena, permitting prediction and accurate simulation of complex (emergent) biological behaviors" (16). "Emergent" is the term most often used to describe the integrated features observed of a system.

Being the systems biology approach based on scientific evidence, the methodological quality of the data can be assured and considered reliable, by analogy with Directive 2001/83/EC. The only fundamental difference is that in a systems biology approach the mechanisms of action of the compound can be inferred from the observed change in the relevant physiological function of the biological system interrogated. Thus, even in the absence of a specifically targeted mechanism the assessment of the product in a proper clinical setting should not be delayed. It has been recently discussed at several levels that there should be a new concerted effort to overcome methodological obstacles that hinder advances in natural products research and in fact the application of "system biology methods" and the advancement of "omics-based" technologies is highly recommended (17).

This attitude pushes forward the knowledge of the history of natural products as sources of medicine and drives towards the discovery of multiple target signature clusters of biological pathways modulated by the complex effects of natural products.

Integrating big data calculations relative to each component of a complex mixture is a first step, although an approximation, since this computation cannot take into account the intermolecular interactions among all components, which influences its mechanism of action.

This mechanism of action cannot be described as pharmacologic as we know it because it cannot be defined by a specific target.

It may be approximated to a physiological mechanism however the best identifier so far can be "non targeted".

A tentative example of the substantial difference between the two definitions can be found in **(table II).**

Table II. Pharmacological and non targeted modes of action and regulatory compliance.

	Pharmacological mode of action	Non targeted mode of action
Active substance	API Active pharmaceutical ingredient	Complex mixture of substances (concerted activities)
Main characteristic	Targeted interaction between a molecule and its specific receptor or targeted effector.	Complex interactions with the human body which bring changes to physiological functions in a way that cannot be pinpointed at the single target/receptor level.
Definition	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. (Meddev, 10).	A set of multiple interactions between the many components of a complex substance and their receptors, interacting among each other in a way that cannot be individually determined.
Matching model of representation	Key-lock interactions of a selected single molecule The target is the receptor	Systems biology / systems medicine The target can only be the function.
Therapeutic effect	Yes	Yes
Regulatory reference when a therapeutic effect is reached	Directive 2001/83/EC	Regulation 2017/745 (Medical Device Regulation).

Conclusions

The growing incidence of "syndromes" and the lack of satisfying treatments requires innovation in all fields of therapeutics. Complex substances, such as natural substances, have always been a source of therapeutic products. Until recently, isolating specific molecules from natural substances was the only way to develop new treatments.

However, keeping the complexity needs to be the new state of the art, while ensuring the necessary safety and efficacy. This requires both adequate experimental models as well as an adequate regulatory framework. The regulatory framework seems to be Regulation 2017/745/EC regarding medical devices. The Regulation explicitly acknowledges medical devices made of substances and envisages these products to act systemically, as highlighted by Rule 21, indicating that the non-pharmacological mechanisms of action go beyond the chemical and physical modes of action to encompass a the "non targeted mode of action" as described in this article. Such an approach will allow the clinical testing of the proposed substance-based devices providing the evidence based medicine data for the clinical application, while the system biology analysis will allow to define the non-targeted mode of action and the biological signature of the intervention as well as the appropriate models for the experimental preclinical investigation of the substance based medical devices. All academic, regulatory authorities and industrial researcher involved in biomedical and clinical research including but not limited to pharmacologists are invited to make the discussion thrive.

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