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EDITORIAL Open Access

Medical Devices made of substances: opportunities and challenges

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The Medical Device (MD) Regulation was officially published in Europe May on 5th, 2017 (https://eur-lex.europa.eu/legalcontent/EN/TXT/?uri=CELEX:02017R0745-20170505) introducing a completely new governance into all aspects of the lifecycle of a MD.

As referred to in the author's contributions, the new regulation should have been applied from May 26, 2020, but has been postponed to May 26, 2021 due to the Coronavirus (https://www.europarl.europa.eu/doceo/document/TA-9-2020-0053_EH.pdf). The healthcare system, the scientific research community and the industrial sector should be prepared to accept the challenges of this profound regulatory change and be ready to transform this change into opportunities for innovation and therapeutic improvement.

The new regulation recognizes and directly addresses a topic of utmost importance to pharmacologists, i.e. "Devices that are composed of substances or of combinations of substances". In fact, as clearly stated in the paper by Racchi and Govoni, "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".

Furthermore, Regulation 2017/745, identifies a specific classification rule (Rule 21) for medical devices made of substances, that is even more intriguing for pharmacologists. Indeed, Rule 21 specifically states:

"Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:

— class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;

— class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;

— ….*omissis*.

The intended purpose for medical devices made of substances is a therapeutic effect (an MD is used for treatment or alleviation of disease); however it "does not achieve its principal intended action by pharmacological, immunological or metabolic means".

We can thus affirm that the Regulation 2017/745, by changing the legislation on MD, has built a structured system in the interest of the patient. In fact, clinical data required to claim any "intended purpose" have been straightened and the safety of the device should be confirmed by a post-market clinical follow-up.
This is a big challenge indeed for pharmacologists. Basic and clinical pharmacologists will be asked to address a series of relevant points:

- the «pharmacological mode of action» and the «non-pharmacological modes of action» should be defined as clearly as possible;
- an evolution of the interpretation of the mechanism of action of substances / complex substances is necessary, since they de facto do not fit the pharmacological model;
- pharmacologists can contribute to this evolution together with regulators, to ensure very best innovation in therapy, within the strictest safety and efficacy standards.

As the Italian Society of Pharmacology, we would like to accept this challenge, first of all by informing the pharmacological community of the changes and opportunities associated with Regulation 2017/745 and secondly by opening up a constructive forum of discussion.
We certainly need to keep an open mind when approaching these topics and avoid to being held back simply by the fear of change or by prejudice. Instead, we need to continue to search and call for convincing scientific and clinical evidence.
In fact, we all know that a huge number of people are using products of unproven efficacy and safety. We are also aware that the drug regulatory system is too rigid for products such as natural complex substances. In this respect, the regulation raises the standard of evidence required to demonstrate safety and efficacy for M.D., based on risk/benefit evaluations. Likely, the regulation will reduce the availability of products of unproven efficacy and will positively impact on the patient's health.
Basic and clinical pharmacologists should collaborate in order to describe and possibly clarify the inside of that "black box", i.e. the "non- pharmacological mechanism", responsible for the documented therapeutic effect of a medical device made of substances. This special issue of Pharmadvances, the official journal of the Italian Society of Pharmacology, aims to be the Forum for this discussion.
The issue contains an article by **Racchi** and **Govoni** and seven commentaries to their paper.
Racchi and Govoni, distinguished pharmacologists at the University of Pavia (Italy), discuss how regulatory documents in the European Union, distinguish "medical devices" from "medicinal products" according to the principal mechanism of action of the product. The correct interpretation of terms such as "pharmacological, immunological and metabolic mechanism of action", have important regulatory implications.
Their main message is "to attract 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".

Marcella Marletta, former Director at the Directorate General for Medical Devices and Pharmaceutical Services, Ministry of Health and **Walter Ricciardi**, President of the Istituto Superiore di Sanità in the years 2014-2018, both highlight the importance that this regulation has for the development of new, innovative, highly needed, low risk therapeutic products and how it will most likely increase and strengthen confidence in the Medical Devices safety among EU healthcare professionals, patients and consumers. They have followed Regulation 2017/745 in its complete evolution.
Paolo Sassone-Corsi, Center for Epigenetics and Metabolism, School of Medicine, University of California, Irvine (USA) discusses how recent technical advances in the field of omics- technologies-, will enable researchers to decipher biological phenomena and thus understand the consequences of the interaction of a complex substance with the human body on a systemic, holistic scale.

Salvatore De Masi, head of clinical research at the Meyer Pediatric Hospital (Florence, Italy) makes an interesting reflection on the gap between the mechanism of action and the therapeutic effect.

Jacques Buxeraud, Honorary and Emeritus Professor, Medicinal Chemistry Department, Faculty of Pharmacy, University of Limoges (France), comments on the systemic approach to the patient considered holistically,

while **Enrico Stefano Corazziari**, Senior Consultant, Department of Gastroenterology, Clinical Institute Humanitas, Rozzano, Milan (Italy) discusses the use of medical devices made of substances in many gastrointestinal disorders and diseases.

Finally, **Fernanda Gellona**, General of Confindustria Medical Devices, gives us an overview of the impact of the industry of medical devices in Italy.
Hopefully, this special issue will stimulate the interest of pharmacologists into pursuing basic and clinical research on Medical devices; we also hope that the working groups on Medical Devices, that are coordinated by the European Commission, will be implemented by experts who have a background in pharmacology. They will certainly contribute to developing the field further.

I would like to warmly thank all the contributors to this special issue.

Alessandro Mugelli
Past President Italian Society of Pharmacology

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ORIGINAL ARTICLE Open Access

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

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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 effect-

ive 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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COMMENTARY Open Access

The new regulation 2017/745: an opportunity for innovation

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As the Regulatory authority of Italy, the Member State which probably has been the most involved in the discussion regarding medical devices made of substances within Regulation 2017/745, I must highlight the importance that this regulation has for the development of new, innovative, highly needed, low risk therapeutic products that comply with the definition of medical devices. In fact, Regulation 2017/745 delineates the formerly called "borderline products" as "medical devices made of substances". These are products which comply with the definition of medical devices and that can well be developed within the medical device regulatory framework, which have brought great health innovation and Member State turnover in many Member States, in the last twenty years of Directive 93/42/EEC.

The Italian competent authority was involved with devotion during its presidency in writing the famous "white book" which has the task of incorporating all the switches from Directive 93/42 into the Regulation. Furthermore, it was involved from the very first proposed version of the Regulation, in September 2012, in the analysis of these "borderline products", to clarify all aspects which would allow their correct scientific and regulatory evaluation in order to allow them to gain access to the market as high quality, safe and efficacious products for the European population. As a regulatory authority participating in the development of the Regulation, we had to evaluate all aspects of these "products" made of substances. They present themselves as syrups, tablets, powders, fluids: it is well evident that macroscopically they resemble products which we are all used to consider "drugs".

For this reason, the tendency has always been to push them into the medicinal product Directive. This was, and still is, the standpoint of several Member States, which believe that the most logical path for natural complex substances is the Traditional Herbal Medicinal Products. This category of products completely waivers all the safety and efficacy requirements of Directive 2001/83 due to their claimed and documented long standing use in Europe and in the world. Logically, this approach has caused the complete stop of all research and innovation in this field. This is because on a microscopic level, complex substances, natural and synthetic, are not compliant with the definition of drugs and they cannot be developed according to the drug regulatory framework.

I have worked decades in both the medicinal product and the medical device departments and I can assuredly say that any product which is not developed according to the model of a single molecule (ie: new chemical entity, isolated chemical class from complex natural substances, biological drugs) cannot comply with the

requirements of the marketing authorization of Directive 2001/83. This is because the very framework of Directive 2001/83 requires the description of the behaviour of the specific active principle, having the pharmacological mechanism of action.
However, the difference between a medicinal product and a medical device made of substances is not intuitive, so discussion among all parties is crucial.
Terms such as "pharmacological mode of action" need to be correctly defined and interpreted, considering both the scientific and the regulatory aspects. In this sense, the interpretation of "pharmacological means" seems to be "a mode of action which can be described according to the Directive 2001/83 model".

In practice, Regulation 2017/745 allows products which cannot be described according to the model delineated by Directive 2001/83 (based on single pharmacologically acting molecules) to be developed with a robust development plan, thus allowing authorities to be confident of the certified products. This is because Regulation looks to many elements of Directive 2001/83 so as to ensure the quality, safety and efficacy aspects consolidated by pharma, but within the medical device risk-based framework.
This combination is the adequate approach for products as diverse and complex as medical devices made of substances wanted by many Member States and by the European Parliament within the Medical Regulation 2017/745, specifically classified with Rule 21 and controlled with General Requirement 12.2.
In particular, the first indent of Rule 21 was expressly included for complex substances, whether natural or synthetic. The European Parliament and several Member States were well conscious that these products, not possibly regulated as drugs, would be either lost to the market or marketed outside the health chain: ie outside the premarket assessment and post market follow up, and the adequate communication of the benefits would be lost. Right now, there is the occasion (and the need) to clarify the interpretation of some other crucial terms for the implementation of Regulation 2017/745, such as all aspects linked to classification Rule 21.
Rule 21 first indent refers to medical devices which need to be absorbed in order to achieve their intended purpose. The concept of absorption linked to efficacy needs to be discussed in case of complex substances, as well as the concept of absorption for safety purposes mentioned in Rule 21 second indent. Another delicate issue is the implementation of General Requirement 12.2, which makes reference to Directive 2001/83 for toxicological and ADME aspects not covered by the Regulation. It is quite logical that medical devices made of substances and complex substances have substantially different chemical characterizations, therefore the risk-based-case-by-case approach characteristic of the medical device framework should allow adequate discussion of each situation, also with Competent Authorities and/or Notified Bodies during product development.
As a Competent Authority of a Member State who is leader in the Medical Device field and specialized in medical devices made of substances, knowing also the intent of the European Parliament to promote innovation in health and health technology, my comment is that all reference to Directive 2001/83 should be seen as a check list to guarantee quality, safety and efficacy, but the practical approach must lie within the medical device risk-based approach.

During trilogue, we wisely created a box for medical devices made of substances. Now, as a Member State, I say that we need to wisely allow innovative products to fill this box. Regulation 2017/745 assures quality, safety and efficacy, we must not fear the regulatory innovation which is available today for the certification of medical devices made of substances, including complex substances, which have no other adequate regulatory framework available for them.
Rule 21 first indent allows to gain back the lost cranberry which concretely cannot be a medicinal product but which, under Regulation 2017/745, gives to the Competent Authority, the guarantee of a thorough development, including clinical evidence, and can be available for the European patient who would otherwise recur to repeated antibiotic treatment.

This is a concrete opportunity for an entire family of products based on complex natural and synthetic substances, which could help manage the new emergent illnesses of our time, such as syndromes, dysfunctional ailments and complex pathologies in general. We are at

a crucial point in the history of therapeutic products could be considered medicinal products, but do not actually fit the medicinal product model. We need to decide to let them have their path to market access within the medical device framework or to lose them as it has been done with cranberry and other subtances already. It must be clear that there the rigorous yet flexible medical device framework based on risk and on a case-by-case evaluation is the only regulatory framework concretely allowing their development.

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COMMENTARY Open Access

Commentary on "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"

(Commentary on Racchi M, Govoni S, 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, Pharmadvances, 2020)

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Advances in medical device technology have been very important in recent years, resulting in an increased number of medical devices (M- Ds) estimated approximately in 500,000 different devices in Europe (1). The aims of EU policies with respect to public health include measures to establish and guarantee high standards of quality and safety for MDs. In this context, a new regulation was approved in Europe in May 2017: the Medical Device Regulation (MDR) (2). This new EU MDR (EU 2017/745) goes into effect on May 26, 2020 and governs all aspects of a MD's lifecycle. The new regulation aims to increase and strengthen confidence in the MDs' safety among EU healthcare professionals, patients and consumers.

The purpose of the regulators was to establish a more robust EU legislative framework to revise the current system for MD regulation in Europe. Historically, devices in Europe do not follow an approval process, but receive a conformity assessment by notified bodies, which, if approved, leads to the issue of a CE mark. In the conformity assessment, the goal to be achieved was "safety and performance as expected" (3). This goal is significantly different from the guarantee of safety and efficacy, that represents a standard requirement for public health. Under MDR, the requirements for devices approval, especially for those at high risk, in terms of clinical evidence will become greater to protect our patients.

Another important element of the new regulation concerns the improvement of transparency (4). In fact, the MDR requires that the manufacturer has to publish a summary of safety and clinical performance (SSCP) for

high risk devices and keep it updated on an annual basis. SSCP documents will be available on the European Union medical device database (EUDAMED). This database, previously accessible only to regulators, will now be publicly accessible. This represents an important element of the new system and underlines the need for transparency that is essential to ensure and support informed decisions on the use of new MDs.

In addition, the new MDR provides for the collection of post-marketing clinical follow-up data by manufacturers who will have to publish the results in a periodic safety update report. In parallel, vigilance procedures should be in place to allow the collection and judgment of adverse device events in clinical practice (4). Furthermore, the MDR improves the traceability of MDs by Unique Device Identification number and implant card for some implantable devices (2). Those described and others among the new indications of the MDR promise to offer greater safety for patients. Furthermore, one of the major changes of the MDR is linked to the extended definition of the term "medical device" that now will include products aimed to perform prediction and prognosis of diseases as well as those which do not have a direct medical intent (e.g. disinfection and sterilization products, fillers, condoms, software or implanted devices used for esthetic and cosmetic purposes) (5). In this innovative element characterizing the new regulation there is the inclusion of the 'Medical Devices Made of Substances'. In particular, Regulation 2017/745 identifies a specific classification rule (Rule 21: Substances or combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed) for MDs made of substances (2). This rule introduces MDs made of substances which need to be absorbed in order to achieve their intended action. This is an important similarity with medicinal products that requires the better definition of the differences between the two categories, in order to promote innovative interventions for the treatment of both established and new conditions.

These treatments differ from drugs and rather than having a pharmacological mode of action, they deliver their benefits through other means of action (such as chemical, physical, physiological), which generally have a particularly low risk profile.

Certainly, MDMS represent investments, research and innovation in health but need adequate regulation. Even the MDMS must be supported by scientific evidence for their commercialization. For this reason too, the new MDR represents an important landmark in the regulation of MDs in Europe. Therefore, it will be essential to promote a clear and homogeneous interpretation of the essential terms at the base of regulatory assessment of substance-based products. This represents a challenge for pharmacologists in order to face a complex definition problem both from a theoretical and experimental point of view (6). To give true effect to the MDR, all interested parties need to work together to achieve the high level of safety that patients expect. All these elements will also be necessary with a view to the value-based resources's allocation in our healthcare systems Healthcare. Systems today are under pressure to optimise the use of limited resources, as they face increasing costs associated with technological developments, increasingly complex patients with multiple chronic conditions and changing clinical practice. To meet the challenge to ensure the financial sustainability of universal healthcare and find resources to fund true innovations it becomes essential to switch resources from lower value to higher value healthcare (7). In this context, an useful evidence-based and value-based tool is represented by Health Technology Assessment (HTA). According to WHO (8) HTA is the systematic evaluation of properties, effects, and/or impacts of health technology. Its main purpose is to inform technology-related policy-making in healthcare, and thus improve the uptake of cost-effective new technologies and prevent the uptake of technologies that are of doubtful value for the health system.

HTA as a decision support tool has been most frequently formally established to evaluate pharmaceuticals (9). However, this methodology has been gaining interest also for MDs. Health technologies are essential for a functioning health system. MDs in particular are crucial in the prevention, diagnosis, and treatment of illness and disease, as well as patient rehabilitation. For this reason, it will be essential to improve the application of the HTA methodology, also applying it to the evaluation of the MDs.

This is to achieve the WHO's strategic goal to ensure improved access, quality and use of medical products and technologies (8).

This objective can be achieved with the collaboration and skills of all stakeholders involved: healthcare professionals, institutions, regulatory bodies, policy and decision makers, industry, citizens and patients.

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COMMENTARY Open Access

Omics-based profiling of systemic metabolic networks to decipher non-pharmacological mechanisms of action of natural complex substances

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Introduction

The advent of the new EU Regulation 2017/745 should be welcomed as an exceptional opportunity to realize major advancements in the treatment of human diseases. Indeed, the introduction of a classification rule such as Rule 21 de facto acknowledges the existence and importance of medical devices composed of substances or their combination which, among others, require to be absorbed by the human body in order to achieve their efficacy. This innovative approach provides a much needed regulatory framework capable of defining the process to generate safe and efficacious therapeutic solutions, backed by credible clinical evidence and based on natural complex substances. The therapeutic potential of natural complex substances is known to mankind since millennia, yet, they are nowadays not regarded as source of therapeutic activities as much as they should. The potential compositional variability of natural complex substances and the intrinsically elusive nature of their mechanism of action, historically led to their decline in favor of the adoption of therapeutic solutions based on single molecules, often of synthetic nature, whose properties are very prone to be technically investigated via a reductionist approach. This, in turn, has led to the establishment of the key-lock (quali-quantitatively definable ligandreceptor binding event) model as the paradigm of election for the investigation of the mechanism of action of therapeutic activities.

Accordingly, the legislations concerning therapeutics have been designed to manage solutions based on single synthetic molecules, able to act via a key-lock mechanism, which in regulatory terms has been defined as the "pharmacological mechanism of action". This approach led to the disappearance of natural complex substances from the repertoire of credible therapeutic solutions available for treatment of human disease. The above described set of both technical and regulatory tools, the only one existing thus far, is in fact not applicable to the field of natural complex substances. Since such substances are mixtures of a great variety of chemical entities, in which both structural and functional interactions can occur, their properties (including PD/PK) are not definable as the algebraic sum of the properties of their single molecular components when studied in isolation (in search of a pharmacological mechanism of action), but are typical of the mixture per se. The properties of natural complex substances are therefore called "emerging properties", and quali-quantitative aspects of the mechanism of action underlying their establishment are,

therefore, conceptually inaccessible through studies conducted with the reductionist paradigm of the "pharmacological mechanism of action" framework. It appears evident, then, that at least in regulatory terms the issue of describing the mechanism of action of a natural complex substance should hinge on the concept of "non-pharmacological", and a rather holistic approach to the generation of the data capable of describing it should be undertaken. EU Regulation 2017/745 provides the long-awaited regulatory tool finally capable of considering peculiarities of natural complex substances within a "non-pharmacological" framework. Definitely the regulation provides for the establishment of requirements capable of rendering these substances a credible therapeutic solution. Yet, the set of techniques capable of approaching the issue of the depiction of the "non-pharmacological mechanism of action" of natural complex substances in a holistic fashion is currently left open. Recent technical advances in the field of omics- technologies, though, now enable researchers to decipher biological phenomena, therefore the consequences of the interaction of a substance with the human body, on a systemic, therefore holistic scale. Transcriptomics and metabolomics profiling of body fluids or organs paired to the use of ad hoc designed bioinformatics pipelines can return a comprehensive picture of the network of metabolic interactions occurring on a whole-body scale. Such tools can therefore acquire pivotal importance in the study of the mechanism of action of natural complex substances, which at that scale occurs.
The combination with other informatic approaches (e.g. chemoinformatics) capable of bridging features (among others, for instance, the chemical-physical properties and composition of the substance) to the biological effect exerted by a natural complex substance, will definitely be able to provide a satisfactory depiction of the mechanism of action of the natural complex substance. The following is a discussion of what application of the current state of the art can already enable to achieve.

Circadian rhythms, Homeostasis and Holistic Biology

Homeostasis, as initially described by Claude Bernard (1813-1878), identifies the capacity of higher animals, to maintain internal stability, owing to the coordinated physiological responses of its parts to any situation or stimulus that would tend to disturb its normal condition or function. Circadian (from the Latin "Circa" = around and "Diem" = day) rhythms constitute possibly the most exquisite system in the control of homeostasis. Circadian rhythms are controlled by molecular clocks- intrinsic, time-tracking systems that enable organisms to anticipate environmental changes (such as food availability and predatory pressure), allowing them to adapt their behavior and physiology to the appropriate time of the day. Indeed, the endogenous clock is synchronized to the daily 24-hour cycle generated by the rotation of our planet around its axis. It is worth noting that many fundamental biological processes function under circadian control underlining the relevance of circadian rhythms for whole body physiology and homeostasis. For instance, in humans, sleep/wake cycle, hormonal levels, blood pressure, metabolic reactions etc. are governed by specific endogenous clocks (Asher and Sassone-Corsi, 2015). The suprachiasmatic nucleus (SCN) in the hypothalamus is the master circadian timekeeper and is mainly entrained by light signals, transduced by specialized photoreceptors present in the retina. However, it has been demonstrated that different regions of the brain or peripheral organs, such as liver, intestine and heart also have local clocks, and that their proper function is necessary to regulate and preserve the physiology of every distinct tissue (Schibler and Sassone-Corsi, 2002). The role of the SCN is to keep these local clocks in synchrony, with each other and with the solar cycle, thereby ensuring that physiology across the entire organism is temporally integrated and thus maximally adaptive, although the underlying mechanisms are not well understood. At the cellular level, any biological process driven by endogenous cellular clocks results in oscillatory rhythms in gene expression, metabolism and behavior. The ability to anticipate daily fluctuations in the environment is a critical adaption across all living organisms. While light exposure is a dominant signal for synchronizing circadian clocks with the environment (so-called zeitgeber, from German, meaning time-giver), post-industrial technology has loosened restrictions on human activity that were previously imposed by the solar day. The resulting shift in sleep-wake cycles parallel alterations to the timing of physical activity and dietary intake, which are potent zeitgebers in their own right.
Disruptions in circadian rhythms resulting from our modern lifestyle are associated with familiar afflictions ranging from jet lag to mood and sleep disorders. The correlation of these cycles with human health and disease is well documented, and recent discoveries have re-

inforced their biological importance. Unraveling the mechanisms driving circadian rhythms affirms their central role in physiology, and it has sparked further research to determine how external factors that interfere with our clocks might also influence the pathology of disease. Lifestyle risk factors such as diet and exercise are believed to play a role in the susceptibility of diseases such as diabetes, obesity, cardiovascular disease and cancer (Asher and Sassone-Corsi, 2015). Could the elevation or reduction in disease risk be mediated through our internal biological clocks?

High-throughput Metabolomics reveal system-wide metabolic connections

Understanding the physiological changes associated with oscillations of specific biomarkers is complex as it requires monitoring elaborate networks of metabolites across multiple tissues at various intervals of the circadian cycle. By applying high-throughput metabolomics in multiple mouse tissues we aimed at unraveling how naturally oscillating metabolic processes are integrated in a physiological network (Dyar et al. 2018). Our comprehensive circadian metabolomics resource provides temporal and spatial perspectives on circadian metabolite abundance, revealing the exquisite temporal intra- and inter-tissue circadian communication that exists both under conditions of energy balance and energy imbalance. Importantly, we show how metabolites are linked within and across various tissues over time, and how they are modified by chronic nutrient stress in the form of chronic high fat diet feeding. By globally mapping relative metabolite distribution and abundance over time, in different tissues, and under different nutritional conditions, we have attempted to accurately capture the dynamic nature of tissue metabolism and inter-organ communication over 24 hours. Analyzing the number, amplitude, class, and peak distributions of circadian metabolites in each tissue, we further characterized tissues in terms of their circadian metabolism and defined precise temporal windows of common and tissue-specific metabolic pathways. Finally, our comparative analysis of metabolite correlations within and among tissues highlights coordinated metabolic pathways under physiological and pathological conditions (Dyar et al. 2018).
This work leverages the study of metabolomics as a critical tool to better understand cellular physiology and to reveal connections between external inputs and pathology (Koronowski et al. 2019). The simultaneous evaluation of a comprehensive panel of multi-tissue metabolites – over multiple time intervals, and under varying environmental conditions allows a glimpse of the communication pathways between various organs that are essential to whole-organism homeostasis. In this case, the combined power of metabolomics with sophisticated analysis tools provides novel insight into the underpinnings of metabolic processes linked to phenotypic differences in mice, and it validates the use of this approach to support new discoveries in human health and disease.

Temporal and tissue-specific metabolite signatures: the effects of nutrient stress

Several studies from our team highlight the effect of nutritional abundance on circadian metabolism and demonstrate its relevance to the development and management of metabolic disease. Building on our previous work, we have used a systems biology approach to examine several tissues in the context of energy balance. By comparing the patterns of metabolism under a normal chow diet with conditions of nutrient stress imposed by HFD, they assembled a spatial and temporal atlas of circadian mouse metabolism. The atlas maps hundreds of circadian metabolites, revealing the metabolic connections that control daily oscillations in processes that are often mediated by distal organ systems. Furthermore, the study showed that external factors such as chronic nutrient stress can alter communication and coordination between tissue clocks, resulting in metabolic changes associated with pathology. Detection included a wide range of metabolite classes from 8 tissue types (i.e., serum, liver, skeletal muscle, brain, brown and white fat, and sperm). Alterations in the relative abundance of several metabolites were characteristic of known tissue-specific pathology. For example, carbohydrates comprised 53% of total altered liver metabolites of mice fed normal chow compared with only 8% in the HFD group. Lipid metabolites exhibited an inverse proportion, with 11% altered in mice on normal chow versus 52% in HFD-fed mice. The accumulation of lipids in liver relative to carbohydrates is suggestive of HFD-induced hepatic steatosis and may have relevance to the progression of NASH (non-alcoholic steatohepatitis).
A similar shift in lipid accumulation in skeletal muscle, a prominent glucose sink, suggests the potential for de-

velopment of insulin resistance (Dyar et al. 2018). Notably, several epidemiological studies have correlated an increased risk for insulin resistance and fatty liver with night shift work. To create a visual atlas of the metabolites under study, we have applied algorithms that plotted the significant temporal correlations according to metabolite class and tissue type. The resulting atlas revealed both temporal and tissue-specific signatures of metabolic pathways over the 24-hour cycle. When examining correlations according to metabolite class, serum lipids showed the greatest degree of synchronization with other metabolites under normal chow, consistent with a role for the vasculature in integrating biochemical networks. However, under HFD nutrient stress, these correlations were lost or significantly reduced, affirming the impact of energy balance on circadian misalignment.

Potential applications in personalized medicine

In addition to elucidating key spatial and temporal elements of energy metabolism, our studies provide a model for examining the relationship between other external factors and normal coherent networks across tissues. The proposed model is not limited to examining the effect of nutritional behavior on metabolic disease, or other behavioral interventions such as exercise.

Integrated analysis of the circadian metabolome, possibly by integrating observations from different omics platforms such as genomics, transcriptomics and microbiomics, offer potential for further discovery in disease pathways to reveal novel biomarkers and therapeutic targets, as well as fine-tuning clinical diagnostics. Diagnostic measures and drug dosing are typically scheduled irrespective of circadian metabolism.

Constraints of the clinician's timetable, ensuring appropriate time intervals between medication doses, or the requirements of sample collection (e.g., fasting plasma or morning urine) dictate scheduling rather than coordinating with biological clocks. Many commonly prescribed drugs work by targeting the products of circadian genes, and since their half-lives are often less than 6 hours, timing of administration might have a significant impact on their action or influence potential side effects. Metabolite comparisons across multiple tissues may provide insight that has been missing from studies of single biomarkers that represent only one tissue at a specific time point of the circadian metabolome (Dyar et al. 2018). While the relationship between coordination of peripheral clocks and pathology remains mostly unknown, the circadian atlas we have developed demonstrates how global metabolomics is essential to fill this information gap. Exploiting known oscillations might permit actionable insights including optimization of other external behaviors, improving the accuracy of diagnostics, and targeting specific time points to administer therapeutics. In the future, this same approach could be used on human samples to unlock biological discoveries hidden within the temporal dysregulation of metabolic processes and provide insights to develop personalized chronotherapy.

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Commentary on "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"

(Commentary on Racchi M, Govoni S, 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, Pharmadvances, 2020)

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Introduction

I read with great interest the paper by Racchi and Govoni on the "*Concept of non-pharmacological mechanism of action"*. The authors refer to the new regulation on medical devices (1) especially to the section concerning "medical devices made of substances" (MDMS) and define their mechanism of action as "non-pharmacological", "non-metabolic" and "non-immunological" (in contrast with to the Ph.I.M. rule). This is the starting point for a broad assessment of the pharmacological paradigm that has led, over time, to the perfect coincidence between "mechanism of action" and "therapeutic effect". The key-lock model is the fundamental assumption of the paradigm that aims to infer efficacy from the mechanism of action rather than legitimizing and explaining it through the mechanism of action. MDMS do not respond to the model underlying the pharmacological paradigm and therefore their mechanism of action is defined in negative. This anomaly (2) highlights the complexity of the real interaction between a substance and the human organism and it underlines our substantial lack of knowledge. It is worth noting that the definition of the presumed mechanisms of action is defined by a negative term (non-pharmacological, non-immunological, non-metabolic). The authors explicitly refer to the theory of complexity (3) and its terminology when they mention the new paradigm of system biology and the emerging properties of such systems. Two reflections arise from this interesting work. The first is that in the path of drugs' authorization, the division into phases of the research implies a certain interest for the issue discussed by Racchi. Assessing toxicity of a molecule during Phase I and its activity during Phase II studies certainly implies a great interest in the mechanism of action, reflecting the influence from the pharmacological paradigm (it is not clear how consciously).

However, the authorization process for drugs involves phase III of the clinical study with all its methodological equipment (ITT analysis, blindness, randomization, etc.); this suggests a certain awareness of the existence of a gap between the mechanism of action and the therapeutic effect. This gap should be bridged by phase III studies aiming to collect information on clinical efficacy "as a whole". "As a whole" means the need to confirm clinical efficacy with studies including "environmental" interference (human organism and everything which is outside the key-lock mechanism).

It is probably true that pharmacological research has increasingly neglected the clinical issues in favor of the pharmacokinetic and pharmacodynamic ones, as evidenced by the recent interest dedicated to extrapolation algorithms which should replace phase III studies in the pediatric population (4). The second is that the temptation to reductionism (coincidence between mechanism of action and therapeutic effect) re-emerges in Racchi's purpose of chemical and physical mechanisms (invoked for MDMS), as an alternative to the pharmacological ones, but always referable to a complete predictability of the system. Nothing new in saying that it is necessary to push the reflection on the gap between the mechanism of action and the therapeutic effect beyond the limits imposed by the current pharmacological paradigm. If the phase III studies already include an all-round evaluation of the complex interaction between substance and human organism, these create an experimental setting that excludes interaction with the "external" environment, which is, instead, considered in pragmatic studies.

Non-recent documents suggest this interest (5), while more recent initiatives relating to the importance of "patients reported outcome-PRO" reveal an opposite trend compared to the paradigmatic one, imbued with values, social components, etc. that increase the distance between the therapeutic effect and the mechanism of action (6). I believe that we should not to give up at looking for an explanation, i.e. the mechanism of action, for the therapeutic effect, but we should be deeply aware that the adventure of knowledge proceeds with the information it has inside, the order of which is sometime bizarre and irrational.

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From conventional drug therapy to a broader systemic view: openness towards new and revised landmarks

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The gastrointestinal tract is the most frequently used way of access for any type of oral therapies and a preferential one for Medical Devices Made of Substances. The so-called complex diseases, which represent a huge part of medical activity, generally result from the complex interaction between biological, psychological, genetic and environmental factors. In fact, approaching the disease from the perspective of the symptom or dysfunction of a single receptor does not always make it possible to effectively manage the patient in all her/his complexity. A systemic approach that considers the whole patient on a totality, capable of regulating her/himself to maintain a homeostatic balance allows to act both on the symptoms and on the signals resulting from all of the organism's interactions, without seeking to identify cause-and-effect relationships. The Medical Devices Made of Substances (MDMS), whose physiological non-pharmacological mechanisms of action allow to regulate the homeostatic balance of the organism, seem particularly useful to complement our therapeutic arsenal. Our knowledge in physiology combined with our better understanding of the pathophysiological mechanisms of the main functions of the organism should encourage us, pharmacologists, doctors and competent health authorities, to take another look both on the way to apprehend medicine and on the evaluation of therapeutic products and their regulatory requirements to access the market.

Towards a paradigm shift in care

Medicine is undergoing profound changes. Acute diseases are gradually supplanted by chronic diseases, themselves generally induced by the lifestyle inherent in our modern society and the growing ageing of the population. Infectious diseases, which, for a long time, have been a major cause of morbidity and mortality, are being better and better controlled.

On the other hand, there appeared, in greater number, so-called complex diseases which now represent a huge part of medical activity, with multifactorial origins, at the same time biological, psychological, genetic and environmental and mechanisms of occurrence which are still little known (1). Typically, this is the case with type 2 diabetes, high blood pressure, congestive heart failure or even digestive problems, whose pharmacological treatments have become considerably more complex over the

past ten years. It is also not uncommon for patients to have multiple complex illnesses simultaneously, which further complicates the disease management. Approaching the disease from the perspective of the main receptor dysfunction based on the targeted symptom does not always make it possible to effectively manage the patient in all its complexity. This approach is reductive and explains the current difficulties to an efficient care management. A systemic approach to the patient that takes into account the dynamic interactions between the impaired functions and their effects rather than the individual receptors correlated to the symptoms appears fundamental to both control the symptoms and rebalance the physiological processes, without attempting the cause-and-effect relationships. This approach, which overturns the traditional landmarks of medicine, acts both on the symptoms and also on the signals resulting from all of the organism's interactions in a system of complex, multiple and circular causalities. In the gastrointestinal system and more specifically in Irritable Bowel Syndrome, an extra-digestive complaint may be the cause and / or the consequence of the disorders. Indeed, central signals such as stress modulate motor skills and digestive permeability. Conversely, digestive events such as fermentation of food in the colon stimulate certain structures of the digestive barrier and activate nervous networks or digestive secretions which are all signals transmitted to the central nervous system.

Thus, a more suitable approach, such as the strengthening of the digestive epithelial barrier, is more and more preferred and shows the limits of the approach targeted on a receptor (2,3). Karl Ludwig von Bertalanffy (1901-1972) has already criticized the reductionism of the natural sciences and said that "living organisms do not follow the same rules as physics" and therefore "we cannot reduce the biological, behavioral and social at the physical level": the first are open systems and the last is a closed system.

He highlighted the need to get out of mechanics to move towards relativity and complexity.

He proposed to consider the observed phenomena as "systems or sets of elements interrelated with each other and with the environment" (4).

From Pharmacology to therapy: opportunities and perspectives

The Medical Devices Made of Substances (MDMS) with a non-pharmacological mechanism of action to regulate the homeostatic balance of the organism seem particularly interesting and useful to complement our therapeutic arsenal. As Dr. Marco Racchi mentioned their "non-targeted" and non-pharmacological mechanism of action appear to be closer to a physiological mechanism of action (5). Some authors even speak of a therapeutic revolution. These complex substances scientifically validated according to the criteria of Evidence-Based Medicine cannot be assimilated to drugs because of their physiological and non-pharmacological mechanism of action. As Dr. Marco Racchi points out "In so far as the aim is the same: to correct a disorder that interferes with the healthy functioning of the body, it is time to enhance the concept of mechanism of action" (6). From a therapeutic point of view, we cannot deny the very close correlation that exists between substance-based medical devices and drugs. Moreover, their definitions overlap.

These products are likely to have the same indication (treatment or prevention of diseases) but the mechanism of action by which they achieve their own therapeutic effect is different. In the history of therapeutic, there are already drugs with a non-pharmacological, immunological or metabolic mechanism of action.

For example, drugs with an antacid effect and drugs with a laxative effect. These drugs are under the same regulation of drugs with a pharmacological mechanism of action.

This should make us reflect! On the other hand, innovative solutions with a non-pharmacological mechanism of action have not been developed under these conditions. So how can we accept today that these innovative solutions, which may have the same effect...but a different mechanism of action, are under the same pharmaceutical legislation?

In the development of a drug, we mainly focus on its molecular mechanism of action. Would it not be appropriate now to focus on the mechanism of physiological action, when the therapeutic objective is to relieve sym-

ptoms or a functioning of our organism which has been altered? Isn't it time to change our vision of molecular pharmacology and also our vision of non-pharmacological mechanism of action?

Our knowledge in physiology combined with our better understanding of the pathophysiological mechanisms of the main functions of the organism should encourage us, pharmacologists, doctors and competent health authorities, to take another look both on the way to apprehend medicine and on the evaluation of therapeutic products and their regulatory requirements to access the market.

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Medical devices made of substances in the management of patients with gastrointestinal diseases

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The gastrointestinal tract is the most frequently used way of access for any type of oral therapies and a preferential one for Medical Devices Made of Substances (MDMS) which can accomplish their therapeutic activities at three different levels:1) within the lumen, 2) on the epithelial barrier, and 3) systemically, after being absorbed. Many gastrointestinal disorders and diseases benefit of MDMSs to be used as add-on treatment to pharmacological agents, substitution of medicine that are either ineffective or causing unbearable side effects and in several conditions in which medical treatment is not available or cannot be utilized. The best clinical indication of MDMS is in patients with chronic gastrointestinal diseases caused by multifactorial factors that cannot be properly tackled by a medicinal product acting on a single receptor whereas a medical device made of complex or natural substances, devoid of receptor effect, can profitably and synergically act on several different pathogenetic mechanisms.

Introduction

Many gastrointestinal disorders and diseases benefit of medical device made of substances (MDMS) and their therapeutic use precedes since long time the recent official statements by governmental agencies defining them for the different mechanism of action from the medicinal products, which is, as explained in the article by Racchi and Govoni published in this issue of the Journal, non- pharmacological, non- metabolic and non-immunological. It is well known the historical use of antacids and osmotic laxatives that exert their action within the gastrointestinal lumen outside of, and without any interaction with, the organism. The digestive tract, not differently from the skin and the respiratory system, has a fundamental function as a barrier to separate the organism from the outside environment of the lumen and has offered so far a great opportunity for medical products to exert beneficial effects by acting either within the lumen and/or on the epithelial barrier being, thus, devoid of any pharmacological, metabolic, and immunological effect on the organism. From now on, however, the recent European Rule 21 2017/745/EC recognizes that MDMS can act also following systemic administration and absorption (1) to include those complex products that exert multiple reactions with the human body not acting at a single target/receptor level. Hence, in addition to the luminal area and vast epithelial barrier, the gastrointestinal tract offers also the great absorptive capability to handle MDMS. In clinical prac-

tice the main indications of MDMS are for add-on treatment to pharmacological agents, substitution of medicine that are either ineffective or causing unbearable side effects and in several conditions in which medical treatment is not available or cannot be utilized. One or more of the above-mentioned limitations of the medical agents often occur in the treatment of chronic or recurrent diseases that, being chronic by definition, defy a ultimate resolution. In addition, chronic diseases usually have multifactorial pathogenetic factors that cannot be tackled alone by a medicine that, by acting on a single receptor, would limit its effect on one of the many pathogenetic factors. Differently from a medicine, a MDMS does not have a receptor effect and, moreover, can be made of complex substances which can synergically act on several different pathogenetic mechanisms. Probably the best example of a chronic gastroenterological condition in which MDMSs find a useful indication is for heartburn and dyspeptic symptoms. Despite the widely accepted medical treatment based on gastric acid reduction with antacids, H_2 receptor antagonist and PPI, the response rate. In these conditions is far from satisfactory. We now know that the pathophysiologic mechanism of heartburn is much more complex than gastroesophageal acid reflux and other factors such as the non-acid reflux, the wide intercellular spaces of the esophageal epithelium leading to a reflux-induced immune and antioxidant sensibilization of the esophageal peripheral nerve fibers (2-3) are not responsive to an acid suppressive treatment. Thirty percent of gastroesophageal reflux patients with endoscopic evidence of esophagitis do not respond to PPI, and in those who respond and obtain mucosal healing with initial PPI treatment, long-term PPI treatment will progressively loose the benefit of the symptomatic response and the mucosal healing (4). Forty per cent of non-erosive reflux disease (NERD) patients and all functional heartburn patients do not respond to PPI treatment (5). PPI cannot be used during pregnancy and are strongly discouraged in infancy. Side effects of short-term PPI treatment are infrequent and usually well tolerated, however in a few patient unbearable side effects force to stop the treatment. In patients with specific diseases such as decompensated cirrhosis or osteoporosis, long-term treatment with PPI is discouraged and in many of these cases it cannot be used (6-7). Even less effective are the medicinal products on the symptoms of functional dyspepsia for which PPI are the first indication according to the actual international guidelines although they offer clinical benefit in no more than 35% of the patients (8). This explains why products not acting with pharmacological, metabolic and immunological means have been used historically in all these conditions of heartburn and dyspeptic symptoms. The first attempts were made, with limited benefit, using antacid substances by simply buffering the gastric acid secretion; more recently, in the attempt to tackle more efficiently one or more pathophysiological factors of heartburn and dyspeptic symptoms, medical devices were developed to oppose the reflux of gastric contents into the esophagus or to reinforce the esophageal and gastric epithelial barrier. Nowadays, the possibility for a medical device to be made from natural substances, and hence with more components acting in synergy, enables to create a complex compound having, at the same time, an epithelial barrier protection as well as antacid and antioxidant activities. As a matter of fact, such medical devices find their clinical application as add-on treatment to not fully effective PPI therapy, in patients not responding to PPI or with unbearable PPI side effects, during pregnancy, in childhood and whenever PPI are contraindicated or not tolerated. Being widely available, a practical use of a medical device is also possible for mild or infrequent episodes of heartburn and dyspeptic symptoms in everyday life. Another gastrointestinal chronic condition with limited therapeutic response is the Irritable Bowel Syndrome (IBS). IBS has different symptomatic expressions and, traditionally, the treatment is directed to the more bothering symptom, be either abdominal pain, or diarrhea or constipation (9). However, despite this approach is the most widely applied, it offers only a limited and temporary benefit for the main symptom, without improving or even aggravating the other disturbances of the syndrome. So, treating the pain with antispasmodics makes constipation worse, and, viceversa, a stimulant laxative for constipation can aggravate abdominal pain. In recent years, several molecules with specific receptor activity, such as guanylate cyclase-C agonist and $5HT_4$ agonist for IBS-Constipation, $5HT_3$-antagonist and opioid-receptor

agonist/antagonist for IBS-Diarrhea, have been developed but their limited efficacy and frequent, and sometimes unbearable, side-effects have limited their use as second-line therapy and in a minority of patients. The mutifactorial pathogenesis of IBS recognizes as the main mechanisms of the syndrome the increased permeability of the epithelial barrier and a low-grade mucosal inflammation. The luminal environment, with bacteria, viruses, fungi, food degradation products and many other antigens, is normally controlled by the epithelial barrier. Whenever barrier permeability increases, the stimulant luminal components activate the mucosal immune system and ROS and thus triggers the enteric nervous system, the neuro-muscular reflexes and enhances the sensitivity of the afferent nervous fibers leading to the clinical expression of pain and altered gut contractions and secretion. Likewise physical and psychological stress can, via nervous and humoral brain-gut connection, activate the mucosal immune system and increase epithelial barrier permeability The low grade inflammation increases the barrier permeability that, in turn, maintains the mucosal inflammation in a vicious cycle that may progressively lead to the severe symptomatic expression of the syndrome (10). In IBS, a complex MDMS made of natural substances can target the main pathophysiological factors aiming to reinforce the epithelial barrier and to have ant-inflammatory and antioxidant activities. Complex MDMS can likewise target multiple mechanisms in other functional intestinal disorders such as Functional Constipation and Functional Diarrhea, being efficient while avoiding the usual side effects of the habitual pharmacological armamentarium. In addition, the minimal side effects and the lack of receptor ligands make MDMSs the ideal products as add-on treatment in the therapeutic management of patients with inflammatory bowel disease who, despite inflammatory remission with antinflammatory drugs, may still present bowel dysfunction and abdominal pain. The minimal side effects and the lack of receptor ligands make likewise MDMS useful in patients with polypathology and polypharmacology as they may substitute, or be added to, some of the receptor targeting drugs.

In conclusion, the multiple physiological mechanisms that can be targeted by MDMS, and even more by complex MDMS made of natural substances, make these medical devices largely used in clinical practice in an ample spectrum of medical conditions. The luminal space and the epithelial barrier of the gastrointestinal tract are natural and amenable non-receptor targets for MDMS that find their main indications in a wide spectrum of chronic gastrointestinal disorders and diseases in which medicinal products exerting their mechanism of action by receptors ligands have limited therapeutic efficacy and are not devoid of relevant adverse effects.

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Medical Devices based on substances

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The world of Medical Devices is not only a brand new and innovative sector but it is also a fascinating, very fascinating world, because every time we look back we see that it is putting us in situations that were not considered in the past or were considered in a different way. There is extraordinary value in this sector, the most suitable example of such value are Medical Devices made of substances (MDMS). Here I try to get to the core of this sector, its features, its opportunities and the challenges on which we have been working greatly with other associations in Europe and in Italy.

Italy, first of all the Ministry of Health (MoH), is highly qualified in the sector of Medical Devices and more specifically in MDMS.

Referring to the new regulation, we have to work with national and European institutions in order to stand up for ourselves and to ensure that the peculiarity of these products be considered.

We have been standing up to safeguard a growing market, because this means jobs, investments, wellbeing and appeal. At the same time, it is a sector that offers efficient therapeutic solutions and these new therapeutic solutions are very important. Therefore, I think it is a great opportunity for all EU citizens. I would like to give a glance to the industry of Medical Devices in Italy. We are talking about 5,000 companies, more than 76,000 employees, more than 11 billion turnover: it is a sector that has nothing to envy to other sectors that are more widely known, in the community, and are considered more precious. We also have other characteristics like a very high rate of education among our employees, given the sector. We have a strong presence of women. So again, as a sector, from this point of view, we try to be really at the forefront. Italy is the first European biomedical pole of manufacturing in the sector of Medical Devices.

Inside the diversified world of Medical Devices, we find those that are based on substances.

This kind of products is certainly one of the most important news in the European Regulation. They represent a new opportunity of care, that both medical and technological sciences are providing to be available to people.

Studies done in the last years demonstrate that these are not drugs, even when they have the same intended use. They are with full right Medical Devices.

How is it possible? Because they have different mechanisms of action from those required for drugs (the pharmacological mode of action). Companies invested and plan to increase the investments in specific studies to demonstrate this situation. We need to have a case by case approach based on experimental evidence.

At present, more than 4,000 companies are operating in the supply chain of medical devices. In MDMS we have 600 companies for a market that is worth more than 950 million Euros, with a very important market share accounting for 28%. The pieces sold per year are 75.4 millions, accounting for 22% of the overall market share for this kind of use and purposes. We point out that also the big pharmaceutical companies are starting to be

present in the market of Medical Devices made of substances. So, if we analyse this market, we see that it is constantly growing. We can see how the potential of MDMS has increased compared to OTCs. This sector is expanding constantly.

It is a constantly evolving market moving from 331 million Euros in 2010, to about more than 950 million in 2019.

The number of references that have been classified as Medical Devices is increasing, it has more than doubled over these years. From 1,002 references in 2010, we went to 2,620 only in 2019 (1). About 190 new references were launched as Medical Devices in 2019 (1). Therefore, this is an opportunity for innovation. Brands present in our everyday life, are now drawing the attention of the biggest pharmaceutical multi-nationals, not only the Italian ones, but also the foreign ones.

We took a specific case, the cough case in Italy, to show how the market has grown in Italy. In 2011, 66% were mucolytic drugs, and 27% were sedative drugs (3), while the Medical Device was just a small residual share, accounting for 7%.

In 2019, 18 years later, the share of Medical Devices grew up to 24%. The cough case is a quite relevant and important case study on the potential of medical devices for therapeutic innovation. So what does it mean? It means that there is a strong expansion going on, 80 references in 2019, 25 launched in the last year. As we hinted above, all the main multi-nationals have penetrated this market. These companies, many of which foreign, have here in Italy an important market share for these MDMS. This means that our country is open to this kind of innovation. Some products can be traded here if they do not find a "mentally" open door in the country of origin.

This is a positive trend. There is sound competition here, good competition, that should not be hindered by legislative prohibitions that might somehow impair the dissemination of these products. From this point of view once again, the choice of physicians on the one hand, but most of all, of the patients, is self-evident. This is true also about other kinds of Medical Devices. If the final user, the citizen, the patient, can choose, that is sound competition. The patient knows whether that substance, that Medical Device, is working or not. If it has a certain level of efficacy, he or she is going to buy the product. It is self-evident. Industry investing, it is creating job opportunities, finally, it is creating culture. I think that in the world of Medical Devices, being that they originate from a combination of knowledge of every kind, a world of culture, science, knowledge, is extremely important. So once again, our Association supports strict regulations, but these regulations have to be suitable. Let us welcome a responsive market that welcomes innovation because that is the actual core mission of this industry and its products. So let us support this therapeutic, industrial and cultural trend, which is thankfully growing. Therefore, in a moment in which we have to provide answers to many health needs and wellbeing needs, we have to give a safe answer in terms of products, a suitable answer in terms of distribution, and quality. I think that the Italian market is at the forefront in this regard, and we hope to keep on with this performance.

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