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# Il concetto di meccanismo non farmacologico: le sfide per il farmacologo

Marco Racchi - Università degli Studi di Pavia


# The problem with definitions

EXPERT REVIEW OF MEDICAL DEVICES, 2016  
<http://dx.doi.org/10.1080/17434440.2016.1224644>



REVIEW

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

Marco Racchi <sup>a</sup>, Stefano Govoni<sup>a</sup>, Adele Lucchelli<sup>a</sup>, Laura Capone<sup>b</sup> and Emiliano Giovagnoni<sup>b</sup>

<sup>a</sup>Department of Drug Sciences, University of Pavia, Pavia, Italy; <sup>b</sup>Aboca S.p.A., Regulatory Division, Sansepolcro (AR), Italy

## **Definition of medical device**

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".

# Mechanism of action and therapeutic effect

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

We find it necessary to draw close attention to and define the concept of 'mechanism of action' because it still comes instinctive to confuse between the mechanism of action of a substance and its effect.

**Therapeutic effect**  
**vs**  
**Mechanism of action**

# What is a therapeutic effect?

The European Court of Justice ruled that *a therapeutic effect is an appreciable modification of physiological functions* (European Communities, Court of Justice, 2009), where ‘appreciable modification’ is understood as a change that can be considered such as to *shift the function in question from a pathological condition (which may be measurable with appropriate parameters) to a normal condition*

# Appreciable modifications - therefore - therapeutic effects

- a vaccine that induces an immune reaction against the inactivated microorganism administered by injection; the measurable parameter is the presence of antibodies specific for the microorganism in question.
- an imbalance among the mechanisms that regulate arterial blood pressure brought back into balance by one or more antihypertensive medicinal products; the measurable parameter is arterial blood pressure.
- hydration of the skin in cases of skin diseases, such as atopic dermatitis; the measurable parameter is trans-epidermal water loss and skin irritation.
- a substance that does not allow formation of biofilm of bacteria on surfaces by inhibiting adhesion; the measurable parameter is evidence of microbiological colonization.

*It is relevant that in the examples indicated the 'mechanism of action' and the 'therapeutic effect' are clearly different concepts. All examples report therapeutic effects, but the first two are achieved through a pharmacological mode of action, the second two through a non pharmacological one.*



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**Ph. I. M.**

Effect in man	Ph.I.M. mechanism of action	Non-Ph.I.M. mechanism of action
Antacid	Antagonist of the H <sub>2</sub> histamine receptor (ranitidine) Inhibition of the Na <sup>+</sup> /H <sup>+</sup> ATPase pump (omeprazole)	Neutralization of the H <sup>+</sup> ion (acid-base action)
Anti inflammatory	Inhibition of cyclooxygenase (NSAIDS) Inhibition of proinflammatory gene expression (glucocorticoids)	Chemical reactions with noxious agents (scavenging of free radicals, chelation of pro-oxidant metals, complexation / denaturation of proinflammatory proteins). Formation of a protective barrier to limit contact between tissue and external or internal irritating agents
Laxative effect	Pharmacologically induced water movement toward the lumen of the intestine (Lubiprostone)	Passive water movement toward the lumen and retention of fluids in the intestine (glycerol, mannitol, other osmotic agents...)
Increase of excretion of dietary fats	Specific inhibition of lipase	Capture of lipids in the intestine
Limitation of microbial contamination	Specific interference with microbial metabolism/reproduction (antibiotics)	Limitation of contact between tissue (skin or mucosae) and other surfaces and external or internal pathogenic agents Modification of the microenvironment

## **Overall we propose to the legislators the following general paradigm:**

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

1. mention of a targeted and specific interaction with a cellular constituent directly and specifically linked to chemical signaling pathways between and within cells (specificity of the interaction)
2. mention that such modification brings about significant changes to the connected biological pathway (transduction of the signal) (it is important not to confuse biological pathway with physiological /pathological function, which would be the effect!)
3. avoid reference to the concept of “indirect” since it would lead to confusion between mechanism of action and therapeutic effect,
4. avoid reference to the entity of the result on the physiological or pathological function since it may create confusion between mechanism of action and therapeutic effect. This aspect is defined elsewhere in the definition of both the medical device and the medicinal product,
5. avoid excessive list of examples within the definition since it may be confusing .

**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
<i>Pharmacological mechanism of action</i>	<p>“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.</p> <p>Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect.</p>	<p>“Pharmacological means” is understood as a <u>TARGETED</u> 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.</p> <p>Although not a completely reliable criterion, the presence of a dose–response correlation is indicative of a pharmacological effect.</p>

# **The problem with experimental demonstration**

## **4.19. Glycerin suppositories**

### **- Background:**

This product is used to relieve occasional constipation. Glycerin suppositories act as a hyperosmotic laxative by drawing water into the intestine. This effect usually results in a bowel movement. Glycerin suppositories act by increasing the transportation of electrolytes through the bowel membrane (osmotic effect) and by stimulating nerve endings of rectum triggering defecation reflex (stimulant effect). In this case an osmotic process leads to a metabolic effect while the stimulant effect is considered as a pharmacological mode of action.

### **- Outcome:**

Glycerin suppositories are a product intended to treat and prevent constipation that act via a metabolic and pharmacological mode of action and should not be qualified as a medical device.





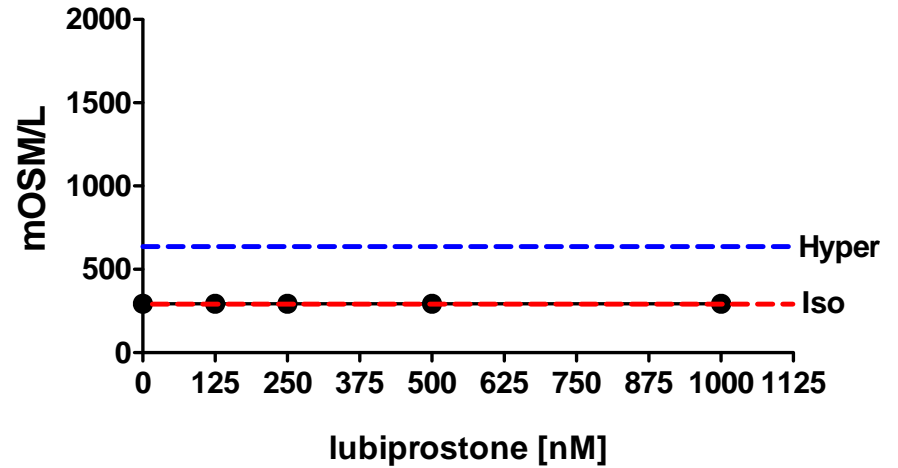
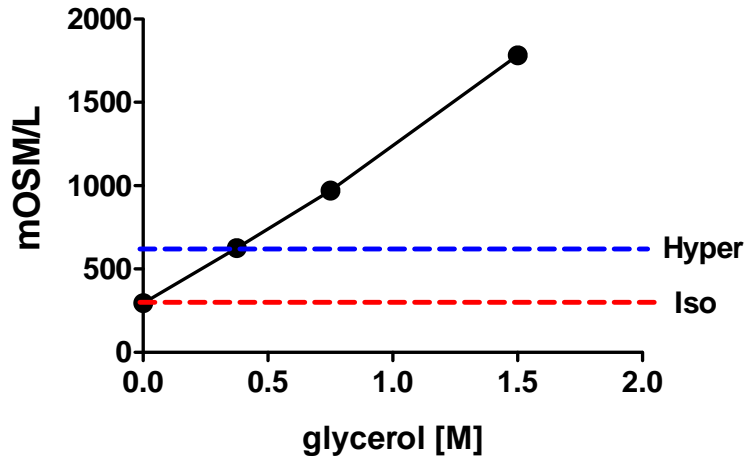
# Experimental Paradigm for the Assessment of the Non-pharmacological Mechanism of Action in Medical Device Classification: The Example of Glycerine as Laxative

*Claudia Sardi<sup>1†</sup>, Stefano Garetto<sup>1†</sup>, Laura Capone<sup>2</sup>, Valentina Galbiati<sup>3</sup>, Marco Racchi<sup>4</sup>, Stefano Govoni<sup>4</sup>, Emiliano Giovagnoni<sup>2</sup> and Jacopo Lucci<sup>1\*</sup>*

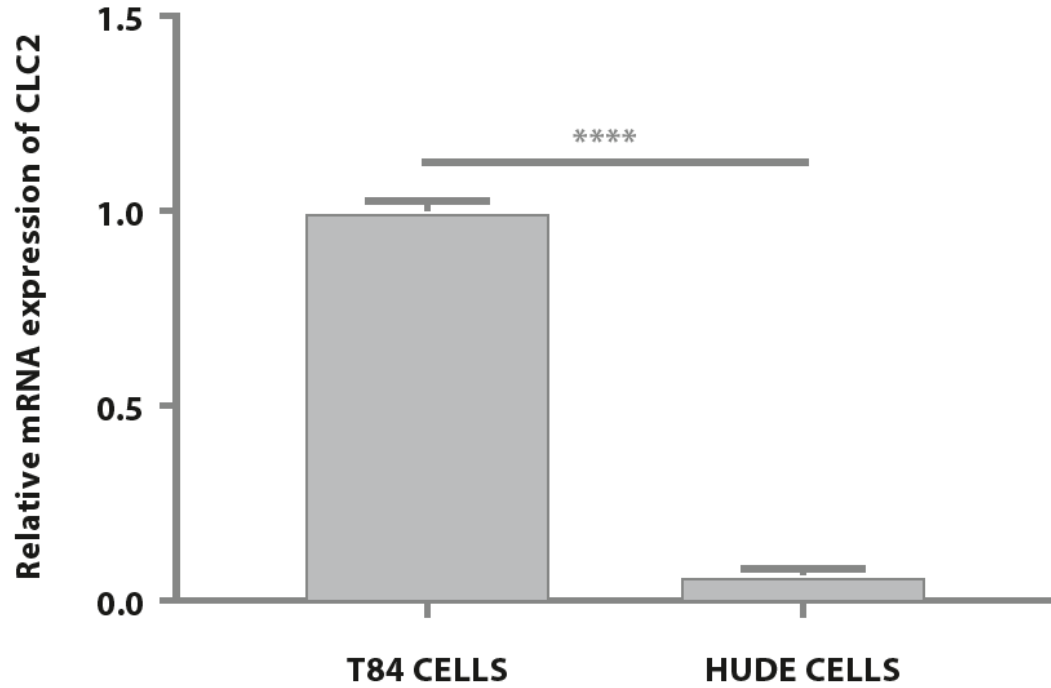
# Aims and purposes

We aimed to design an experimental set up to demonstrate the difference between the mechanism of action of two substances used commonly for the treatment of constipation, lubiprostone (example of medicinal product) and glycerine (example of medical device). By implementing cellular models and molecular analyses we demonstrate the difference in their mechanism of action. This set up can be considered an example on the possibility to define a paradigm for the case by case study of the mechanism of action of substances and combination of substances in medical devices.

# Osmolarities of operative solutions of Glycerol and Lubiprostone

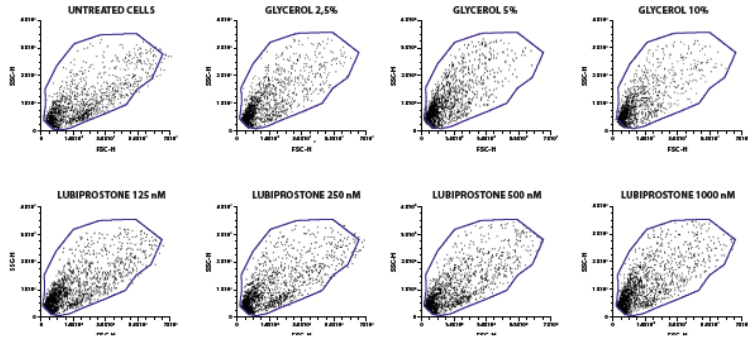
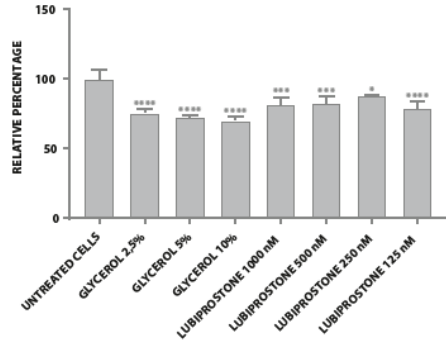


## T84 and HuDe gene expression analysis of CLC-2

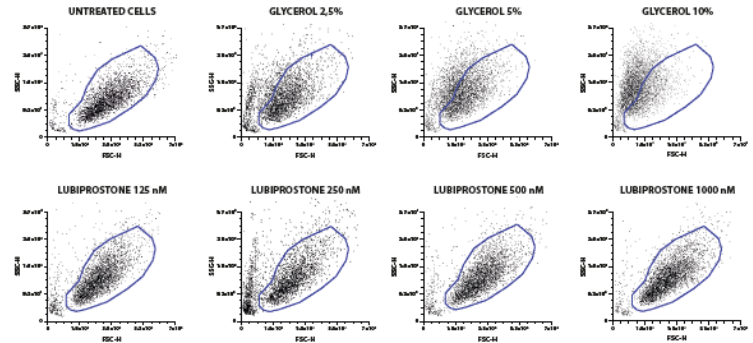
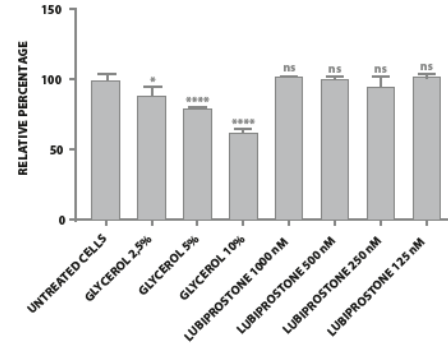


# Effects of treatments on cell volume

T84



HUDE



# Medical Devices made of substances and complex substances

- Medical devices made of natural complex substances often have more than one mechanism of action concurring to the claimed therapeutic effect.
- Natural substances are regulated by legislations as different as food, dietary supplements, medical devices and medicinal products.
- Natural substances are composed of a very high number of molecules, acting in synchrony, in a way that is best represented by the concept of “system” which is in fact different than the sum of its components.

# Special Issue – Medical Devices made of substances: opportunities and challenges

Reviews

 Thieme

## Medical Devices Made of Substances: Possible Innovation and Opportunities for Complex Natural Products<sup>#</sup>

OPEN  
ACCESS



Authors

Anna Rita Bilia<sup>1</sup>, Enrico Stefano Corazziari<sup>2</sup>, Stefano Govoni<sup>3</sup>, Alessandro Mugelli<sup>4</sup>, Marco Racchi<sup>3</sup>

...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...

Ricciardi W (2020) 01s: 16-18

<https://doi.org/10.36118/pharmadvances.01.2020.04s>

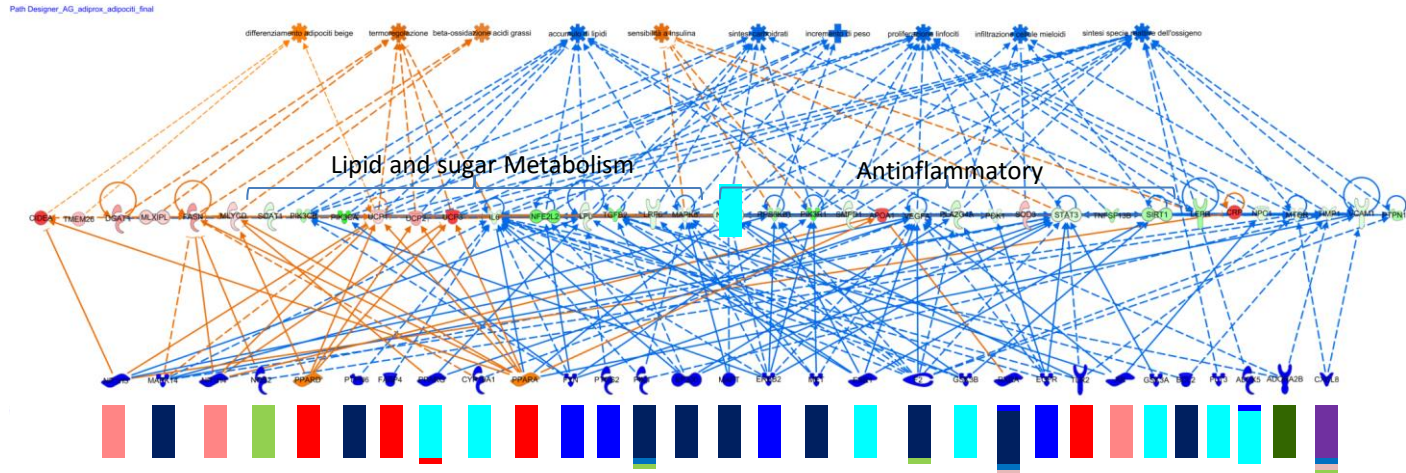
It appears evident, then, that at least in regulatory terms the issue of describing the mechanism of action of a natural complex substance should hinge on the concept of “non-pharmacological”, and a rather holistic approach to the generation of the data capable of describing it should be undertaken.

Sassone Corsi P (2020) 01s: 19-22

<https://doi.org/10.36118/pharmadvances.01.2020.05s>



# Prediction of the mechanism of action of a complex combination of substances



The effect of multiple components of a complex mixture are exerted on several targets and each may engage numerous nodes of signalling. This type of investigation reveals that the effect is multitarget and redundant. That is why natural molecules should not be purified down to the single component: that is when they lose efficacy!

► **Table 1** Pharmacological and nontargeted modes of action and regulatory compliance [15].

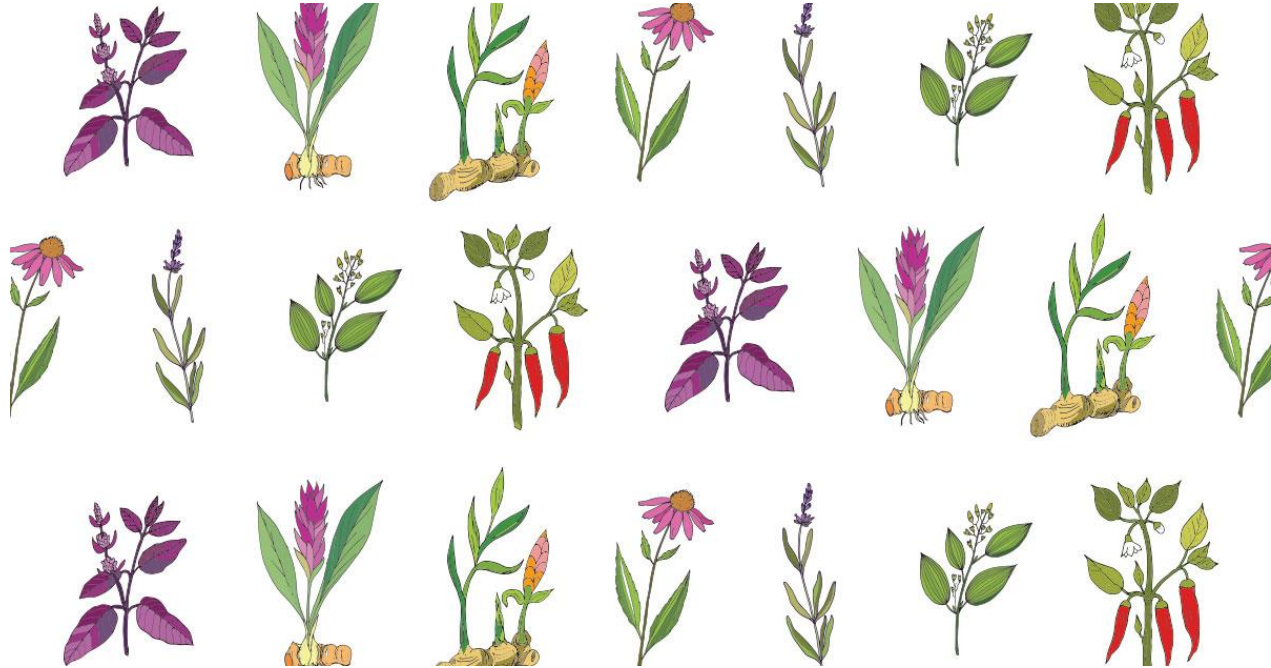
	<b>Pharmacological mode of action</b>	<b>Non-targeted mode of action</b>
Active substance	Active pharmaceutical ingredient (API)	Complex mixture of substances (concerted activities)
Main characteristic	Targeted interaction between a molecule and its specific receptor or targeted effector.	Complex interactions with the human body that 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 [14].	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)

Bilia AR, Corazziari ES, Govoni S, Mugelli A, Racchi M. Medical Devices Made of Substances: Possible Innovation and Opportunities for Complex Natural Products. *Planta Med.* 2021 Aug 6. doi: 10.1055/a-1511-8558.

**Multitarget  
Signature  
Cluster  
Assay**

**M**ultitarget  
**S**ignature  
**C**luster

# Nature is an Orchestra



We must understand its **MuSiC**

# Conclusion

Overall our investigation suggests that current definitions of "pharmacological means" reported on the European Meddev2. 1/3 rev 3 and the more extensive elaboration of these definitions proposed in our recent papers, can serve as a grid for experimental pharmacologists to establish the pharmacological/non pharmacological mechanisms of action of a substance or combination of substances.