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PROBLEMS OF CLASSIFICATION, SAFETY ASSESSMENT AND RISK MANAGEMENT OF MEDICAL DEVICES WITH BIOLOGICALLY ACTIVE SUBSTANCES

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The aim *of the work was to investigate scientific and technical approaches for ensuring biological safety and classifying medical devices containing biologically active substances in the context of new international standards and regulatory requirements.*

Materials and methods. *The study includes an analysis of the current regulatory landscape, including Regulation (EU) 2017/745, international standards ISO 10993, and guidance documents from the Medical Device Coordination Group (MDCG). Classification specificities of medical devices containing biologically active substances were examined, taking into account their mechanism of action. Approaches to biocompatibility assessment and systemic risk analysis were reviewed using the Weight of Evidence (WoE) concept.*

Results. *Key differences between the classification of medical devices under Directive 93/42/EEC and Regulation (EU) 2017/745 were analysed. The study identified specific aspects of biocompatibility assessment for medical devices containing biologically active substances, as well as challenges related to the standardisation of their physicochemical characteristics. Examples were provided to distinguish between medicinal products and medical devices based on their mechanism of action. The implementation of modern methods for assessing medical devices' safety and regulatory status was also examined.*

Conclusions. *The new regulatory requirements, in particular the provisions of Regulation (EU) 2017/745, significantly impact the classification and biological safety assessment of medical devices containing biologically active substances. An adaptation of the biocompatibility assessment methods was proposed, considering modern trends and the "Weight of Evidence" approach. The study highlights the need to update Ukraine's national regulatory framework to align with European standards and to introduce clearer methodological approaches to differentiate between medicinal products and medical devices*

Keywords: *medical devices, biologically active substances, biocompatibility assessment, medical device classification, regulatory requirements, ISO 10993, Regulation (EU) 2017/745, risk management, safety assessment methods, preclinical studies, regulatory framework harmonization*

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1. Introduction

Ensuring the safety and effectiveness of medical devices containing biologically active substances is becoming an increasingly relevant challenge in today's regulatory environment. In particular, Regulation (EU) 2017/745 introduces new classification requirements for such devices to enhance patient safety and increase the transparency of conformity assessment processes. One of the key aspects to consider in developing and evaluating medical devices is their mechanism of action, which does not always conform to traditional pharmacological, immunological, or metabolic models [1].

Despite the stringent regulatory framework, assessing biocompatibility for biomaterials used in medical devices remains a complex task due to multiple factors, including the material's chemical properties and physical characteristics, the type of tissue/site of interaction, and the duration of exposure. Although international standards such as ISO 10993-1:2018 are commonly applied to demonstrate compliance with regulatory requirements necessary for market approval or the initiation of clinical trials, they may lack sufficient detail or fail to address all aspects of risk management, particularly in material selection and the development of appropriate *in vitro* biocompatibility screening methods for medical device manufacturing [2]. This necessitates adapting biocompatibility assessment methods, such as the Weight of Evidence (WoE) approach, which integrates various data types while evaluating their reliability and consistency. In this context, a clear distinction between medical devices and medicinal products, based on their primary mode of action, is also particularly important.

Ensuring the stability and safety of medical devices composed of biologically active substances is a complex yet essential process that begins at the development stage. Such devices require well-defined and reliable quality parameters that allow for the consistent monitoring of product properties and the safety of each batch.

Quality control of biologically active substances of natural origin demands a specialized approach, as their characteristics differ significantly from synthetic components and are often influenced by multiple variables, such as environmental conditions, processing methods, and raw material storage. The development of appropriate specifications for such devices may be based on pharmaceutical principles, but must also account for the unique requirements of biologically active substances.

1. 1. Terminological issues in regulatory translation

In preparing this article, we utilized English-language materials from regulatory documents, scientific journal articles, and other sources. It has been observed that certain nuances arise in the translation of these materials, some of which have also been reflected in regulatory documents approved and implemented by Ukrainian legislators. We would like to highlight some of these subtle yet important distinctions.

The term "substance", which appears in regulatory documents such as Council Directive 93/42/EEC [3], Regulation (EU) 2017/745 [4], and guidance documents issued by the Medical Device Coordination Group (MDCG) [5, 6], as well as in the Technical Regulation on Medical Devices, approved by Cabinet of Ministers Resolution No. 753 of October 2, 2013 [7], has been translated into Ukrainian as "compound".

It should be noted that the term "compound" is not explicitly defined in the Technical Regulation on Medical Devices or in the Methodological Recommendations for the Application of the Technical Regulation on Medical Devices, approved by Order of the Ministry of Health of Ukraine No. 142 of January 22, 2020 [8]. Furthermore, this definition is absent from current legislative acts related to medicinal products. The only occurrence of an official definition appears in the Law of Ukraine "On Medicinal Products" No. 2469-IX, dated July 28, 2022 [9], which will come into force on January 1, 2027. This definition is a literal translation of "substance".

As a result, a regulatory gap emerges due to the absence of a consistent definition and the varying translations of key terms across different legislative acts in the healthcare sector. This inconsistency could create challenges in the future, particularly when interpreting European regulatory documents during their implementation into Ukrainian legislation. Additionally, discrepancies within Ukraine's regulatory framework may arise, potentially leading to legal ambiguities and misinterpretations in the harmonization process.

With the adoption of Regulation (EU) 2017/745 [4], the term "Substance-based medical devices" (SBMD) has emerged in English-language regulatory discourse. However, its translation into Ukrainian remains rather general and does not fully convey the specific nature of such medical devices due to the absence of a standardized regulatory definition for "substance".

In this article, to emphasize the unique aspects of the new classification rules for medical devices, the term "substance" will be translated as "biologically active substances". We believe this translation will be more comprehensible to scientists and will better highlight the nuances and distinctions in terminology where necessary.

Another notable nuance observed in the Technical Regulation on Medical Devices is the direct translation of the term "means" from Council Directive 93/42/EEC [3]. This term appears alongside "pharmacological", "immunological", and "metabolic", yet there is no officially approved definition for it in Ukrainian regulatory documents.

Referring to the regulatory framework for medicinal products, it becomes evident that "pharmacological", "metabolic", and "immunological" are commonly associated with "actions" rather than "means", which is a more familiar phrasing for scientists. As previously mentioned, Ukrainian legislation lacks official definitions for "pharmacological, metabolic, and immunological actions" or "means", further complicating the consistency of terminology.

The absence of clear definitions and explanatory guidance for developers, manufacturers, and conformity assessment experts on frequently arising issues may negatively impact the introduction of innovative healthcare products. It would be beneficial if Ukrainian regulators adopted a similar approach to their European counterparts by developing and implementing guidelines and recommendations.

For example, during the implementation and transition to Regulation (EU) 2017/745 [4], the Medical Device Coordination Group (MDCG) was established. This group develops not only guidelines that clarify aspects not explicitly described in the Regulation but also "Questions and Answers" (Q&A) documents, which provide responses to common queries from stakeholders.

Introducing a similar practice in Ukraine could enhance regulatory clarity, facilitate compliance for manufacturers, and support the smooth adoption of new legislative requirements.

The minor translation nuances and lack of definitions described above may not seem like obstacles to the development and market introduction of new medical devices at first glance. However, such issues could become significant barriers in the present and future for advancing medical device development and manufacturing.

The rigid structure of market surveillance authorities prevents them from taking more or fewer steps than those explicitly stated in the Technical Regulation on Medical Devices. This limitation creates regulatory inflexibility, making it difficult to adapt to innovations in the medical device sector.

Given these identified terminological challenges, it would be appropriate to update the Technical Regulation on Medical Devices in Ukraine to align it with modern European standards. Additionally, implementing guidelines and explanatory materials – similar to European recommendations – could facilitate regulatory clarity, innovation, and growth within the Ukrainian medical device industry.

2. Research planning (methodology)

The study focuses on analyzing modern approaches to ensuring biological safety and the classification of medical devices containing biologically active substances, considering new international standards and regulatory requirements. The research planning involved several key stages, ensuring a systematic approach to addressing the set objectives.

To achieve the research goals, a comprehensive approach was applied, which included:

– theoretical analysis – a review of scientific sources on the methodology for assessing biological safety and regulatory classification of medical devices;

– systematization and comparative analysis – generalizing data on classification and regulatory requirements across different countries;

– logical analysis – drawing conclusions on the effectiveness of existing approaches and providing recommendations for improving regulatory requirements.

Based on the collected data, the research was divided into the following stages:

– analysis of current international standards and regulatory frameworks;

– identification of criteria for assessing the biological safety of medical devices;

– systematization of classification requirements for devices containing biologically active components;

– development of recommendations for improving regulatory policies.

3. Materials and methods

The regulatory framework analysis was conducted based on international standards, including ISO 10993 (biocompatibility assessment), Regulation (EU) 2017/745 (Medical Device Regulation in the EU), and the current Ukrainian legislation on medical devices. Special attention was given to regulatory requirements concerning the classification of medical devices containing biologically active substances, their safety and effectiveness assessment, and the procedure for conformity to technical regulations.

For data collection and analysis, open-access electronic resources were utilized, including scientometric databases such as Google Scholar, PubMed, Clarivate, Web of Science, Scopus, and others. Additionally, electronic repositories of higher educational institutions and scientific institutions containing dissertations, scientific articles, and other publications, including the results of their own previous research, were analysed.

The following methods were applied in the research process: information retrieval – systematic search of regulatory and scientific sources, theoretical analysis and systematization – review and structuring of relevant scientific literature, logical analysis – formulation of conclusions based on collected data, critical analysis of regulatory documentation and requirements – evaluation of the existing regulatory framework and its applicability to medical devices containing biologically active substances.

4. Research results

4. 1. Comparison of differences in the definition of "Medical Device" and the classification of medical devices under Directive 93/42/EEC and Regulation (EU) 2017/745

Regulation (EU) 2017/745 (hereinafter referred to as the Regulation) introduces certain changes in comparison with Council Directive 93/42/EEC (hereinafter referred to as the Directive) in the definition of a medical device. These modifications were implemented by the EU to enhance the safety, quality, and effectiveness of medical devices. The key differences between the definitions are presented in Table 1.

The Regulation expands and clarifies the definition of medical devices, introducing the following key changes:

– more precise definition. The concept of a medical device is formulated in greater detail. Notably, the definition now explicitly includes products intended for the sterilization, cleaning, and disinfection of medical devices and their accessories;

– innovations. The Regulation introduces requirements concerning new technologies, such as software. Unlike the Directive, which primarily focused on traditional devices, the Regulation recognizes standalone software as a separate category of medical devices if it is used independently for medical purposes, such as diagnosis or treatment [10];

– expansion. According to IAF MD 9:2023 [11], the Regulation extends technical application areas to include aesthetic and cosmetic products, preventing their market placement without proper conformity assessment. This applies explicitly to dermal fillers, lasers for liposuction, and skin resurfacing [12].

The Regulation significantly expands and updates the classification of medical devices compared to the Directive. It not only accounts for modern technologies and innovations but also introduces stricter safety requirements, including additional subclasses and new rules for software-based and combination devices.

The Regulation establishes 22 classification rules for determining risk class (Annex VIII of the Regulation), compared to 18 rules outlined in the Directive. The classification of medical devices under the Regulation is based on four main risk classes – I, IIa, IIb, and III – considering the intended purpose, invasiveness, duration of use, and inherent risks associated with the device [13].

Within Class I medical devices, there are four subcategories:

– non-custom-made, non-investigational devices (I);

– sterile devices (Is);

– devices with a measuring function (Im);

– reusable surgical instruments (Ir).

Examples of classification based on the specific characteristics of medical devices are shown in Fig. 1.

The main differences between the classification rules for medical devices outlined in the Directive and the Regulation lie in the greater level of detail, clarification, and adaptation of classification to new technologies and risks, as illustrated in Fig. 2.

Table 1

Comparison of the Definition of "Medical Device" Between the Directive and the Regulation

Directive 93/42/EEC (1993) [3]	Regulation (EU) 2017/745 (2017) [4]
Medical device – any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, *including software* necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: – diagnosis, prevention, monitoring, treatment, or alleviation of disease; – diagnosis, monitoring, treatment, alleviation, or compensation for an injury or disability; – investigation, replacement, or modification of the anatomy or a physiological process; – control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means	Medical device – any instrument, apparatus, appliance, *software, implant, reagent,* material, or other article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: – diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease; – diagnosis, monitoring, treatment, alleviation, or compensation for an injury or disability; – investigation, replacement, or modification of the anatomy or a physiological or pathological process or condition; *– providing information through in vitro examination of specimens derived from the human body, including donated organs, blood, and tissues;* and which does not achieve its principal intended action by pharmacological, immunological, or metabolic means in or on the human body, but which may be assisted in its function by such means. Medical devices also include: – devices for control or support of conception; *– products specifically intended for cleaning, disinfection, or sterilization of medical devices and their accessories*

	Class I	Class I Special functions	Class IIa	Class IIb	Class III
Examples:	*Plasters* *Disposable Gloves* *Otoscope* *Dermatoscope*	**Is:** sterile dressing, sterile syringe (without needle) **Im:** thermometers, measuring cups **Ir:** Medical tweezers, scalpels	Short-term corrective contact lenses, feeding pumps, polymer film dressings	Corrective long-term contact lenses, urinary catheters, ventilators, infusion pumps, radiation-emitting devices, such as therapeutic X-ray sources	Heart valves, cardiac pacemakers, drug-eluting stents
Risk	Low → High				

Fig. 1. Examples of classification based on the specific characteristics of medical devices according to the Regulation [12, 14]

The Regulation introduces more structured classification rules that consider new types of devices and modern technologies [16]. For example, software intended to provide information for decision-making with diagnostic or therapeutic purposes, or software designed for monitoring physiological processes (Rule 11 of the Regulation) is now considered a medical device, except in cases where it does not analyze data or alter the patient's treatment, dosage, or other medical parameters [17].

Additionally, medical devices containing nanomaterials now have a dedicated classification rule (Rule 19) due to their potential impact on health, particularly regarding toxicity and interaction with cells [18].

Special attention is given to the classification of devices composed of substances or mixtures of substances (biologically active substances) that have biological activity and are intended for administration into the body through an orifice (e.g., oral or nasal cavity) or for application to the skin (Rule 21). This category has been the subject of intensive discussions among regulators and scientific experts due to the unique nature of their mechanism of action and associated risks [19–21].

Another key innovation concerns the classification of active therapeutic devices with an integrated or embedded diagnostic function (Rule 22). This rule was introduced to enhance the classification system for medical devices compared to previous regulatory provisions and to ensure a proper risk assessment for their use. Embedded diagnostic functions can significantly affect the safety and effectiveness of therapy, requiring additional considerations for potential risks such as false diagnoses, incorrect therapeutic decisions, or insufficient measurement accuracy [22].

Although the Regulation establishes classification rules for devices containing biologically active substances, certain products have been excluded from its scope. For instance, products containing or consisting of viable biological material or living organisms, including live microorganisms, bacteria, fungi, or viruses, do not fall under the Regulation's scope [23]. As a result, products that previously fell under the Directive, such as probiotic-containing devices, must now comply with other regulatory requirements. However, challenges remain in determining whether a product should be classified as a medical device or a medicinal product, highlighting ongoing regulatory ambiguities [24].

Rules 1 - 4: Non-invasive devices			
Rule 1	**Rule 2**	**Rule 3**	**Rule 4**
No changes	- Addition of 'cells and tissues' to the existing wording - Blood bags moved to Rule 2 of the Regulation from Rule 18 of the Directive	- Adding 'human tissues and cells' to the existing wording - Changing the wording to 'intended for implantation or administration' instead of 'for infusion' - Inclusion of organ storage solutions, IVF media, in the rule, with the appropriate risk class	- Adding 'damaged mucous membrane' to the existing wording - Replacing 'wounds' with skin damage - Covers also invasive devices that come into contact with the damaged mucosa
Rules 5 to 8: Invasive devices			
Rule 5	**Rule 6**	**Rule 7**	**Rule 8**
No changes - just clarifications	- All devices intended to come into direct contact with the heart or central circulatory system are now classified as Class III, as are devices that come into contact with the central nervous system	- All devices intended to come into direct contact with the heart or central circulatory system are now classified as Class III, as are devices that come into contact with the central nervous system	- Implantation devices and accessories - class III - Breast implants and surgical matrices - Class III - Complete and partial joint replacement - class III - Implants for replacement of intervertebral discs or implantable devices in contact with the spine are classified as Class III, with some exceptions (screws, wedges, plates and instruments)
Rules 9 - 13: Active devices			
Rule 9	**Rule 10**	**Rule 11**	**Rule 12**
- Additions to active devices intended to deliver ionising radiation for therapeutic purposes, including devices that control or monitor such devices or that directly affect their operation, are classified as Class IIb - Add-on active devices intended to control, monitor or directly affect the operation of implantable active devices are classified as Class III	- Adding 'monitoring' to diagnostics; - Active devices intended for diagnosis in clinical cases where the patient is in immediate danger are classified as Class IIb	- New rule on software - Classifications range from Class III to Class I	- Rule 11 of the Directive - No changes
			Rule 13
			- Rule 12 of the Directive - No changes

Rules 14 to 18: Special rules				
Rule 14 (Products with medicinal substances)	**Rule 15** (Contraceptives, means to prevent the transmission of STIs)	**Rule 16** (Disinfectants, sterilisers)	**Rule 17** (Devices for recording X-ray diagnostic images)	**Rule 18** (Devices that use drugs of human or animal origin)
- Clarification that a medicinal product may be derived from human blood or plasma - 'Obliged to act' has been removed	- Rule 14 of the Directive - No changes	- Adding sterilants to disinfectants - Disinfectants or sterilisers are only classified as Class IIb if they are used for invasive devices and as the final step in reprocessing	- Rule 16 of the Directive - No changes - wording clarified	- Adding 'cells' to the existing wording - Adding cells and tissues of human origin or derivatives thereof - Exception for contact with intact skin only applies only to animal tissues and does not apply to human tissues or cells

Rules 19 to 22: Special rules			
Rule 19 (Devices incorporating or consisting of nanomaterials)	**Rule 20** (Invasive devices inserted through openings in the body intended for the administration of medicines by inhalation)	**Rule 21** (Devices consisting of substances that are introduced into the body through a body orifice or skin and that are absorbed or locally distributed)	**Rule 22** (Active product with integrated or built-in diagnostic function)
- New rule - Classifications from III to IIa based on impact potential	- The new rule - Classification IIa or IIb - IIb, if they affect the safety and efficacy of the medicinal product or are intended to treat life-threatening conditions	- New rule. - Classification from IIa to III depending on where they are used and whether they or their metabolic products are absorbed	- The new rule -- Class III - Applies only if the following products have a significant impact on patient management - Closed circuit systems or automated external defibrillators

Fig. 2. Comparison of classification rules outlined in the Regulation versus the Directive [15]

4. 2. Problems of classification of medical devices made from biologically active substances

The Regulation introduced a significant innovation for medical devices based on biologically active substances [21], definitively regulating their classification as medical devices. In the context of previous "directive-based" discussions, European-level debates primarily focused on the lack of specific provisions for risk management related to invasiveness and potential toxicity, as well as the absence of a dedicated classification rule that would reflect their level of risk.

To address these concerns, a specific classification rule was introduced that considers where the device performs its action – whether it is introduced into the human body through an orifice or applied to the skin – and whether the substances undergo systemic absorption or remain locally dispersed. These factors were integrated into the Regulation's classification framework [25]. Rule 21 specifically accounts for these unique risks associated with medical devices made from biologically active substances [24].

However, despite the existence of Rule 21, challenges often arise in clearly distinguishing between medicinal products and medical devices due to complex combinations of biologically active substances (e.g., plant-based products) or the lack of consensus on the nature of their primary mode of action [26–28].

For the first time, the concept of local dispersion appears in the Regulation, playing a crucial role in classifying medical devices composed of biologically active substances or mixtures of substances that are introduced into the human body [5, 24]. This innovation highlights the need for a more precise definition of how biologically active substances act in the body to ensure accurate classification.

According to MDCG Guidance 2021-24 [5], local dispersion is defined as: "A state in which substances remain in a specific area of the body without being distributed throughout the organism via the blood and/or lymphatic system".

This concept is crucial for understanding the mechanism of action of certain medical devices. For instance, if a substance is administered locally and does not spread through systemic pathways (blood or lymph), its action remains confined to the specific area where it was introduced.

In 2022, the MDCG 2022-5 guidance "Guidance on the Borderline Between Medical Devices and Medicinal Products Under Regulation (EU) 2017/745 on Medical Devices" [6] was adopted – an important document in the context of the qualification of borderline products, particularly medical devices made from biologically active substances. During the Directive era, the classification of such borderline products relied on the MEEDEV Guidance on Borderline Products [29], which, however, contained a limited number of practical examples for users.

The MDCG 2022-5 [6] examines key issues regarding the use of biologically active substances in medical devices, as the term "substance" itself lacks a clear definition in the Regulation. The Commission refers to the definition of "substance" provided in Directive 2001/83/EC [24, 30] but also emphasizes the importance of distinguishing medical devices from medicinal products based on their mechanism of action and intended purpose [6].

According to Directive 2001/83/EC, a substance is defined as: "Any matter irrespective of its origin, including chemical elements, chemical compounds, or any biological substance (of plant, animal, or microbiological origin)" [30]. Directive 2001/83/EC also defines a medicinal product as: "Any substance or combination of substances presented as having properties for treating or preventing disease in humans; or any substance or combination of substances that may be used to restore, correct, or modify physiological functions by exerting a pharmacological, immunological, or metabolic action, or to establish a medical diagnosis."

It should be noted that even new EU regulatory documents, both for medicinal products and medical devices, do not contain a clear definition of "non-pharmacological" mechanisms of action (and, accordingly, non-immunological or non-metabolic mechanisms) [28]. In practice, such mechanisms in European regulation are generally associated with physical and chemical modes of action [26]. Although the medical purpose of medicinal products and medical devices is clearly defined, the primary distinction lies in their mechanism of action [20]. Unlike medicinal products, the primary intended action of medical devices must not be based on pharmacological, immunological, or metabolic mechanisms (Ph.I.M.) but should instead rely on physical or chemical mechanisms [26, 27]. These mechanisms typically include mechanical action, the creation of physical barriers (e.g., protective films), lubrication, heat transfer, radiation or ultrasound effects, replacement or support of organs or bodily functions, hydration or dehydration, and pH modification [6, 27].

The MDCG 2022-5 guidance [6] defines a pharmacological mechanism of action as: "An interaction, typically at the molecular level, between a substance or its metabolites and a component of the human body (e.g., cell membranes, intracellular structures, RNA, DNA, proteins, extracellular matrix components, blood components, and body fluids), leading to the activation, enhancement, reduction, or blocking of physiological processes or pathological conditions." [28].

Thus, to recognize a mechanism of action as pharmacological, two key factors must be confirmed: 1) the existence of an interaction between the molecule of the substance and a cellular structure of the body, and 2) the presence of a direct physiological response that modulates or blocks processes in the body [27, 24].

The distinction between a medical device and a medicinal product lies not only in their intended purpose but also in their mechanism of action [1]. Both products may share the same therapeutic goal, such as treating the same disease, but differences in their mechanism of action determine their classification [28]. As noted in reviews [26, 28], this differentiation is crucial for properly understanding their functions and intended use.

It should also be considered that, according to Article 2(1) of the Regulation, a medical device may contain biologically active substances with pharmacological, immunological, or metabolic action. Still, these substances must have a supporting role to the primary mechanism of action of the device [27]. The key classification criterion is that the primary action of the product must be physical or chemical rather than pharmacological [26, 31].

There is often misinterpretation between the terms "therapeutic effect" and "mechanism of action", which are not interchangeable concepts [28, 32]. It is important to emphasize that for medical devices containing biologically active substances, understanding the mechanism of action plays a significant role, as it is not always pharmacological [25, 33]. However, there remains a lack of clarity among scientists and regulators regarding how to experimentally demonstrate these non-pharmacological mechanisms of action [32, 33].

To correctly interpret and assess the mechanism of action, it is essential to avoid confusion between "mechanism of action" and "effect", since the body always responds through pharmacological, immunological, or metabolic pathways, even to non-medicinal stimuli. This highlights the need for clear differentiation between these concepts and principles to ensure the proper evaluation of medical devices, particularly regarding their potential influence on physiological processes.

Scientists face several challenges concerning the classification principles of medical devices containing biologically active substances during the development process and market entry. In our view, the mechanism of action of a medical device is influenced by multiple factors, such as dosage, site of application or administration, device formulation, and the type of biologically active substance.

Fig. 3 presents our perspective on the point of intersection and the factors that may influence the mechanism of action, shifting a product into the regulatory framework of either medical devices or medicinal products.

Identifying the key determinant among these variables is critically important for accurately understanding the device's impact on the body. This, in turn, is crucial for its correct regulatory classification as a medical device. An adequate safety and efficacy assessment can be conducted through a thorough analysis of these parameters, ensuring the product's regulatory compliance and proper classification.

Let us consider some examples that illustrate how the same biologically active substance may exhibit a different mechanism of action depending on the correlation of dose, formulation, and site of application/administration.

N-acetylcysteine, by its chemical nature, has a mucolytic effect. Due to its free sulfhydryl group, acetylcysteine breaks disulfide bonds in acidic mucopolysaccharides, leading to the depolymerization of mucus mucoproteins, reducing mucus viscosity, and facilitating the expectoration and clearance of bronchial secretions [34, 35]. N-acetylcysteine products in the form of tablets, oral powders, oral solutions, and injectable solutions are currently classified as medicinal products [36]. However, nasal sprays or solutions for nebulizers and instillations [37, 38] containing N-acetylcysteine may be classified as medical devices due to a different route of administration and product formulation, as they act more locally.

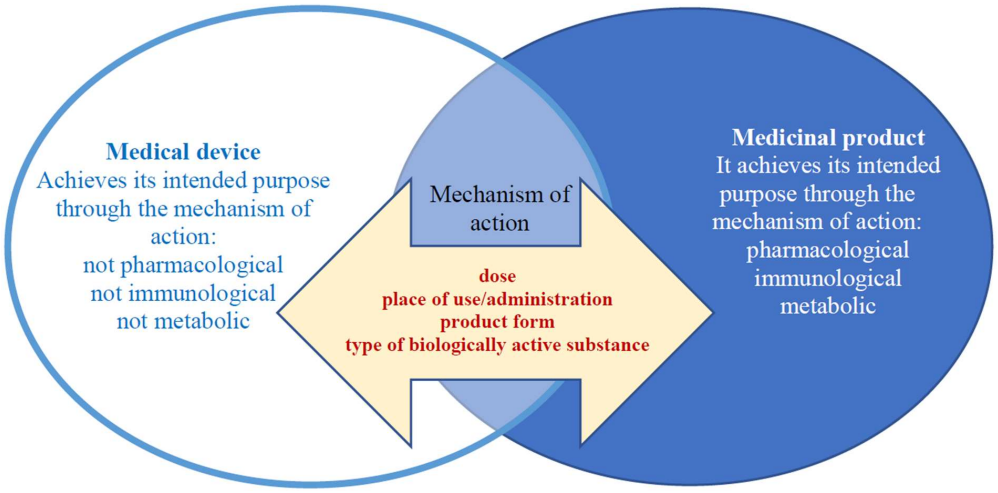

Fig. 3. Point of intersection and factors that may influence the mechanism of action

Another example of a product containing a biologically active substance but classified differently depending on its form and application site is ascorbic acid. In oral or injectable form, products containing ascorbic acid are classified as medicinal products [36]. However, in the form of vaginal tablets with modified release, ascorbic acid can alter the vaginal pH, exerting a physicochemical mechanism of action, and is therefore classified as a medical device [39].

Sodium hyaluronate is a widely used ingredient in both medicinal products and medical devices [40], yet its function and regulatory classification vary depending on its intended use and mechanism of action. In medicinal products, sodium hyaluronate is primarily used for its ability to enhance hydration and promote tissue healing [41]. Its pharmacological action in this case involves binding water and retaining moisture, improving skin, joint, or mucosal elasticity [42, 43]. For example, in dermatology, sodium hyaluronate is used in creams and gels to enhance skin hydration [44].

Sodium hyaluronate is often used as a viscous substance injected into joints to improve lubrication, cushioning, reduce friction, and alleviate pain [45, 46]. In this case, the mechanism of action is physical, as the substance provides space between joint surfaces and does not exert a pharmacological effect [47]. In ophthalmology, sodium hyaluronate in moisturizing gels or artificial tears acts as a hydrating agent, forming a protective film on the eye's surface [48]. This is a mechanical barrier mechanism that reduces irritation and ensures comfort, without an active pharmacological effect [49]. Similarly, sodium hyaluronate functions as a mechanical barrier in gynecological products, where it is used in gels and suppositories to form a protective film on the vaginal mucosa [40].

Citicoline is a unique substance that can perform various functions in the body, depending on the form of administration, dosage, and application method. Its versatility allows citicoline to be used as a medicinal product, dietary supplement, or medical device, as its properties vary based on the use context [49, 50]. In the form of an injectable solution, citicoline is approved as a medicinal product [36]. When administered via injection, it is rapidly metabolized, producing choline, a precursor of acetylcholine, an essential neurotransmitter. In this form, it exerts a pharmacological effect, influencing the central nervous system, improving cognitive functions, memory, and attention [51, 52]. Due to this, citicoline is used for cognitive health support and treatment of certain neurological disorders [53].

In oral form (tablets, capsules), citicoline is classified as a dietary supplement [52]. This form has lower bioavailability than injections but still supports brain function and contributes to overall cognitive enhancement [54]. Citicoline, as a dietary supplement, is used to prevent age-related cognitive decline, as choline, formed during its metabolism, supports the normal function of the nervous system.

In ophthalmic drops, citicoline is used as a medical device, for example, as an adjunct to antihypertensive therapy in patients with glaucoma [55, 56]. In this case, it has a physical or physicochemical mechanism of action, influencing local metabolic processes in the eye and protecting the optic nerve [49]. This mechanism of action does not involve a classical pharmacological effect on the body, allowing citicoline in this form to be classified as a medical device. This example demonstrates how different citicoline formulations may have distinct mechanisms of action depending on their route of administration and dosage [49]. In glaucoma treatment, citicoline acts through a complex interaction involving multiple physiological processes rather than a single molecular target [54]. This highlights that citicoline's effect cannot always be explained by interaction with a specific receptor or target molecule alone.

The above examples illustrate an approach where biologically active substances used in both medicinal products and medical devices can be identified using specific markers. For such substances, determining the mechanism of action and corresponding therapeutic effect is often easier based on the "lock-and-key" model, where a specific molecule interacts with a defined target in the cellular system [54]. This provides a clear mechanism of interaction, where one marker triggers a specific physiological response.

Biologically active substances derived from plant materials require a different approach to defining their mechanism of action. Plant-based raw materials consist of a complex mixture of many biologically active components that act synergistically [57, 58]. Isolating and separating these substances is not only challenging and economically unfeasible but may also reduce their effectiveness due to the loss of synergistic and cumulative effects of other components. The approach of isolating a single marker and studying it as the active component, which is often used in product development under Directive 2001/83/EC [30], does not account for the complex interactions between other components of the mixture, which may be crucial in achieving a specific therapeutic effect [58]. Therefore, such products require a comprehensive evaluation that considers not only a single active component but also the synergistic action of all biologically active substances within the formulation. It is important to note that while the therapeutic effect of these substances may be well known, their mechanism of action cannot be precisely described without significant simplifications [28].

Natural substances are inherently complex, meaning they are composed of a large number of molecules that act synchronously in a way best described by the concept of a "system" [25]. A "system" differs from the sum of its components, as it includes interactions and interconnections between each molecule, as well as emergent properties resulting from intermolecular interactions, such as the chemical and physical behavior of the entire composition, which can only be observed when the system is intact [25, 59].

The lack of a well-founded conceptual model that describes the mechanism of action of natural complex substances may lead to their classification as traditional herbal medicinal products, which, in practice, prevents innovation, as the regulatory framework for such registration is based on the long-term use of a specifically defined extract [25, 60].

An interesting example of a complex product based on plant extracts and natural components is the medical device Policaptil Gel Retard tablet 725 mg [61, 62]. The mechanism of action of this medical device was recognized as non-pharmacological, as its gel-forming ability allows it to physically retain lipids and carbohydrates from the ingested diet [61, 63]. In vivo studies [63] showed that this medical device improved metabolic parameters by modulating the gut microbiome and, as the authors suggest, indirectly influencing gene expression involved in liver metabolism. This demonstrates that even a physical mechanism of action can indirectly affect other bodily systems, exerting pharmacological, immunological, or metabolic effects [64, 65]. This highlights the complexity of establishing a clear mechanism of action for complex naturally occurring biologically active substances.

According to scientists [16, 24, 66], all reactions triggered by complex plant-derived substances, where the marker-trigger does not match the broadly defined "lock-and-key" target model, should be considered from a regulatory perspective as products falling under the Regulation. This includes numerous interactions between complex biologically active substances and the human body, which can only be described through a "systems biology" approach, characterised by a degree of uncertainty stemming from applying statistical modelling tools to knowledge about molecular behaviour in a complex chemical environment [28].

Systems biology is defined as "a scientific approach that combines principles of engineering, mathematics, physics, and informatics with large-scale experimental data to develop a quantitative and deep conceptual understanding of biological phenomena, enabling the prediction and precise modelling of complex biological behaviour" [59]. Thus, systems biology could become a tool for modelling complex interactions of plant extracts at the cellular and organismal levels [25, 67]. These methods may allow for predicting possible therapeutic effects and identifying key mechanisms, even if they do not follow classical pharmacological interactions [59, 68].

Accordingly, plant-derived biologically active substances require a different approach to defining their mechanism of action, as it is represented by the mechanism of action of the entire product rather than a single selected component [69]. Specifically, for medical devices made from biologically active substances of plant origin, reproducible quality [70] is the foundation for consistent efficacy and safety and includes standardization of extraction methods, chemical composition assessment, safety evaluation, and appropriate clinical evidence of effectiveness. However, the theoretical and practical approach to establishing interaction mechanisms with cellular components for such medical devices will differ from those used for products containing a single active substance. It seems crucial that with the adoption of the Regulation and the clarifications provided in MDCG 2022-5 [6], regulatory attitudes toward these products should evolve.

There are already precedents for such regulatory changes, such as oral products containing simethicone, which act through a physicochemical mechanism by reducing the surface tension of gas bubbles, alleviating bloating and pain without pharmacological action [71]. With the introduction of the Regulation, such products are now classified as medical devices, whereas previously they were developed and approved as medicinal products [26].

As of today, considering Regulation (EU) 2017/745 and MDCG 2022-5, developers, scientists, and conformity assessment experts must approach the classification of products containing plant-derived biologically active substances on a case-by-case basis. In some instances, it may be necessary to consult the European Medicines Agency (EMA), the European Chemicals Agency (ECHA), or the European Food Safety Authority (EFSA) to determine the appropriate regulatory status of a product [4, 24].

4. 3. Safety assessment of medical devices made from biologically active substances

Conducting research on the biological evaluation of medical devices made from biologically active substances is not only a compliance requirement of the Regulation but also one of the key processes to ensure their safety and

effectiveness for patients. Such research involves a comprehensive assessment of the interaction between the device materials and the tissues and cells of the body to identify and minimize potential biological risks [72, 73].

The main provisions regarding the evaluation process are outlined in the Regulation and ISO 10993-1:2018 standards [74], which establish mandatory requirements for biological evaluation studies. Unlike the Directive, the Regulation contains detailed and mandatory requirements for biological assessment, especially for devices containing biologically active substances [75]. The Regulation requires consideration of the application method and the activity of such a substance to assess potential risks, including toxicity, immune reactions, and other aspects of biological activity [4].

One of the essential aspects of ensuring the biological safety of medical devices is assessing their biocompatibility and potential impact on the human body. Recently, significant attention has been given to developing new approaches to assessing the biological activity of such materials, particularly through innovative methods for analyzing toxicological profiles and risk assessment [76].

Furthermore, modern research indicates a significant influence of pharmacogenomics on the safety and effectiveness of medical devices containing biologically active substances. Genetic polymorphisms can alter the pharmacokinetics and pharmacodynamics of such chemicals, affecting individual patient responses. This underscores the need to consider personalized approaches when assessing risks and biocompatibility [77].

Additionally, studies on the immunogenicity of medical devices are critically important, as their interaction with the body's immune system can further impact their safety and effectiveness. The possibility of isolating and characterising specific immune responses opens prospects for further research on immune response mechanisms to biologically active components in medical devices [78]. In this context, the potential biological risks associated with hybrid technologies should also be taken into account, including the possibility of immunogenic reactions and their impact on the biocompatibility of medical devices [79]. The introduction of such methods can reduce potential risks and increase the safety of devices containing biologically active substances.

The Regulation and ISO 10993 standards – guiding documents for assessing the biological safety of medical devices – describe a systematic approach to determining the safety of devices for clinical use, based on an analysis of all available safety data [73]. The main stages of this approach include [80]:

1. Assessment of physical and chemical information:

– analysis of the physical and chemical characteristics of device materials, including their specifications and composition of primary and auxiliary substances, manufacturing conditions, and composition of packaging materials used during production;

– consideration of the potential impact of sterilization methods and conditions on device properties. This helps assess the potential release of substances that may affect the device's biological compatibility.

2. Evaluation of biological endpoint testing data:

– analysis of biological data obtained for the materials from which the device is made, similar devices, and the medical device under evaluation. This includes the results of *in chemico*, *in silico*, *in vitro*, and *in vivo* testing;

– this stage involves identifying potential risks associated with materials and assessing their impact on biological compatibility.

3. Review of clinical use and existing clinical data:

– evaluation of expected clinical use scenarios of the device, such as the type of tissue contact and duration of use;

– analysis of existing clinical data related to the use of similar devices, as well as information on their safety history and user complaints [75]. This helps consider potential risks and provides insight into known adverse reactions or successful use cases.

Based on these data, a qualified specialist in toxicology or biocompatibility assesses whether the device is biocompatible for its intended use or whether additional information or research is needed to address residual risks that could impact patient safety [80].

According to ISO 10993 standards, biological evaluation studies must include the following key aspects:

– cytotoxicity (ISO 10993-5:2009) [81]: Testing at the cellular level to assess how a material affects cells;

– sensitization and irritation (ISO 10993-10:2021, ISO 10993-23:2021) [82]: Evaluation of allergic reactions and irritation, especially for substances that may affect the skin or mucous membranes;

– hemocompatibility (ISO 10993-4:2017) [83]: If the device comes into contact with blood, assessing its impact on hemolysis and the coagulation system is necessary;

– toxicological assessment (ISO 10993-11:2017) [84]: This is particularly important for devices containing biologically active substances. It includes assessing potential systemic toxicity, including long-term effects if the substance spreads through blood or tissues.

Evaluating their antimicrobial activity is an essential stage in ensuring the safety and stability of medical devices containing biologically active components. Research results indicate that organic carboxylic acids, such as formic, acetic, propionic, and citric acids, exhibit pronounced antimicrobial activity against several bacterial pathogens responsible for foodborne toxic infections. This suggests their potential use as preservatives to ensure medical devices' microbiological stability and safety with biologically active components [85].

It is important to note that ISO 10993-1:2018 provides recommendations on the required "set" of aspects that need to be determined in biological evaluation studies, depending on the duration of application/contact with the patient, site of application, and method of administration. Cytotoxicity, irritation, and sensitization tests can be called the "Big Three", as determining these three biological effects is required for most medical devices regardless of category, patient contact, and duration of use [74].

Nevertheless, existing ISO standards for ensuring biocompatibility lack comprehensive analysis and consideration of certain specific aspects [86]. For example, ISO 10993-5:2009 [81], which includes cytotoxicity as-

sessment methods for testing cell reactions to biomaterials and their extracts, is not always sufficient for assessing reactions to implanted biomaterials [87, 88]. This limitation is due to the inadequacy of tests that can accurately reproduce in vivo conditions and long-term effects [89].

Additionally, ISO 10993 standards often do not consider unique functional properties that make a device's design or composition distinctive. For instance, in the case of antimicrobial surfaces, many standards do not clearly differentiate between systems that release antimicrobial agents and systems that do not have this effect [80, 90]. This means that additional specific tests, beyond ISO 10993 standards, are often required to verify unique design properties [87].

ISO 10993-1:2018 [74] emphasizes the importance of professional judgment in interpreting biocompatibility requirements and assessing data on the safety of medical devices [73]. However, the document does not provide guidelines for integrating all collected data, complicating the process of forming a comprehensive conclusion about a device's safety. Other regulatory agencies, such as the United States Environmental Protection Agency (USEPA) [91], have developed approaches like the Weight of Evidence (WoE) for environmental assessment and human health risk assessment, which could be considered more comprehensive for the biological evaluation of complex medical devices containing biologically active substances [92, 93]. WoE approaches enable the integration of different types of data, assessing their reliability and consistency to formulate more substantiated conclusions [94].

A comprehensive approach to safety assessment is particularly significant for medical devices made from plant-based compositions. This includes preclinical pharmacological studies demonstrating their biological activity, as well as biocompatibility analysis according to modern regulatory standards such as ISO 10993 and Regulation (EU) 2017/745 [95]. A crucial direction in assessing the safety of medical devices containing biologically active substances is studying the mechanisms of action of their components. A key aspect of such analysis is the examination of molecular mechanisms that ensure therapeutic effects and material biocompatibility. For instance, heparin-binding epidermal growth factor-like growth factor (HB-EGF) exhibits a broad spectrum of biological activity, which is important for regenerative medicine. HB-EGF participates in regulating cell proliferation, differentiation, and migration and inhibits apoptosis. Moreover, it plays a vital role in tissue healing processes, which may be significant for medical devices intended for skin or mucosal restoration. However, considering its involvement in tumor growth mechanisms, evaluating the safety of materials containing HB-EGF or similar growth factors requires special attention and the application of modern risk assessment approaches [96].

The implementation of a systematic approach to the safety assessment of medical devices containing biologically active substances, including the WoE concept, allows for the integration of different types of data to comprehensively determine their safety and efficacy profile. The proposed WoE structure [75, 80] would help systematize and integrate all obtained data, taking into account the device's application context, which would allow:

– a better understanding of the relationship between biocompatibility and actual patient risks;

– avoidance of underestimation or overestimation of risks;

– more accurate and realistic conclusions regarding device safety.

Implementing the WoE approach by manufacturers of medical devices containing biologically active substances can significantly improve the biocompatibility assessment process of such devices, increasing confidence in decision-making regarding their safety for patients [73, 80].

The WoE assessment concept is used to comprehensively assess the biological safety of medical devices. It should be noted that such an approach, for application by qualified experts to evaluate whether a device has an acceptable biocompatibility profile or if additional data or measures are needed to mitigate risks for patients, is also provided in ISO 10993-1:2018 [74, 80, 97].

The overall safety assessment of medical devices can be divided into three general groups, which together provide a comprehensive examination, while WoE allows for the integration of data from these groups:

1. Group 1 – physical characteristics, chemical characteristics, and toxicological risk assessment. Physical characteristics of the device include size, shape, roughness, and other geometric and physical properties of materials in their final form. These parameters can affect biological endpoints, such as hemocompatibility and implantation, as rougher surfaces may increase the likelihood of blood clotting or foreign body reactions [98]. The assessment of physical characteristics is based on project documentation or analytical methods, such as scanning electron microscopy (SEM) and visible light microscopy (VLM) [80]. Comparison with similar devices that have already been approved and have market experience allows avoiding additional testing if physical characteristics are analogous [97].

The chemical profile of a medical device includes information about structural materials, manufacturing processes, packaging, and sterilization. To assess potential chemical impact and risks, the manufacturing conditions, composition of raw materials, and excipients are analyzed [80]. Additionally, chemical characteristics can be used to assess whether changes in materials or manufacturing processes affect the chemical composition of the device that contacts the patient, to the extent that it may impact its safety [99]. If a "paper" assessment is insufficient, quantitative methods such as X-ray photoelectron spectroscopy (XPS), Fourier-transform infrared spectroscopy (FTIR), or analysis of extractables and leachables (E&Ls) are applied to determine the chemical components that may be released during device use [80].

Toxicological Risk Assessment (TRA) is used to determine the likelihood of adverse effects during the clinical use of the device. According to ISO 10993-17:2023 [100], TRA includes four stages [73, 80]:

– hazard assessment (identification of potentially hazardous chemicals);

– exposure assessment (evaluation of the possibility of patient exposure);

– dose-response assessment (determination of the relationship between dose and toxic effects);

– risk characterization (evaluation of actual risk to the patient).

TRA also considers conservative factors, including the assumption that the entire chemical mass is immediately available to the patient, which may sometimes lead to excessively high-risk estimates [101].

Data is considered more reliable if studies comply with ISO 10993-17:2023, ISO 10993-18:2020, ISO/TS 10993-19:2020 [100, 102, 103] standards and yield favourable results [87]. If low values of the margin of safety (MOS) calculation (less than 1) in TRA indicate increased risk, these values can be confirmed by other reliable data (e.g., clinical data) that confirm the absence of adverse effects [80].

2. Group 2 – biological endpoint assessment. ISO 10993-1:2018 provides Table A.1 [74], which defines biological endpoints that should be considered based on the device type and patient contact duration. If some endpoints cannot be assessed using TRA [100], they can be determined through *in vitro* and *in vivo* testing. This allows for the evaluation of potential adverse effects for the patient. It is worth noting that such tests may use extraction conditions that lead to significantly higher doses than a patient would typically receive, ensuring an additional level of safety but sometimes leading to results with no clinical significance [80].

According to WoE [80], a high score is given to tests conducted in compliance with ISO 10993 standards, the American Society for Testing and Materials (ASTM), or Good Laboratory Practice (GLP) with positive results. Failed results or a lack of testing lowers the evaluation score. This is particularly relevant for in vitro analyses, such as cytotoxicity, which are frequently used but may show a high level of sensitivity [87, 104]. Negative test results do not always indicate a direct hazard to the patient, especially for short-term or non-invasive devices.

3. Group 3 – clinical data, safety history, and complaint information. Clinical Evaluation Reports (CER) are key documents confirming medical devices' safety and effectiveness in real clinical conditions [105]. CER includes preclinical studies, scientific research, and post-market surveillance, helping to identify and assess the frequency of adverse effects and undesirable events [4]. Complaint data collected during post-market surveillance can be analyzed to determine risk levels and potential safety signals. Such data is recorded in the Periodic Safety Update Report (PSUR) and the Post-Market Clinical Follow-Up (PMCF) to classify complaint types, allowing for the identification of potential patient safety threats [106].

It is critical to ensure the reliability of complaint data, as not all complaints can be thoroughly classified. Additionally, not all adverse effects can be assessed using complaint data, especially in cases where long-term monitoring (e.g., carcinogenicity) is required [80, 106]. It can be assumed that accumulated complaint data for medical devices with long-term market experience (over 10 years) or large production batches (e.g., more than 100,000 units) will provide more predictive values for determining an acceptable risk level [80].

In the proposed WoE structure [80], a scoring scale was developed for evaluating input data in the biological assessment of medical devices. This scale assigns quantitative scores based on the quality and reliability of each data set, facilitating a comprehensive evaluation of the biocompatibility profile of the device. The higher the score, the lower the likelihood that the device poses a biocompatibility risk, allowing for assessing its patient safety.

It should be noted that WoE does not differentiate between the duration and nature of a device's contact with the body, as the fundamental assumption is compliance with the biological evaluation requirements of ISO 10993-1 [74, 80]. However, devices with short-term or non-invasive contact present a lower risk to patients, and unfavourable results from one category may be less significant for these types of devices than invasive ones [87].

The WoE structure can serve as a tool to ensure consistency in the biological evaluation process, particularly for medical devices containing biologically active substances, and for further regulatory review by providing a set of parameters to address the question, "How much data is enough?" to ensure patient safety [73, 87].

4. 4. Standardisation of physical and chemical parameters of medical devices made from biologically active substances as an element of ensuring patient safety

The foundation of stability and safety for medical devices made from biologically active substances must be established during the development stage [107]. One of the key elements of the evidence base proving that a medical device is safe is clearly defined quality indicators [108], which enable monitoring and confirming quality consistency from batch to batch [109].

Standardization of the physicochemical parameters of medical devices containing biologically active protein-based substances (e.g., recombinant proteins) is of particular importance. Quality control of such substances, including determining their concentration, activity, and stability, is a necessary condition for ensuring the safety and efficacy of the final product. Even minor changes in the physicochemical properties of protein-based substances can significantly impact their therapeutic properties, reducing effectiveness or increasing the risk of adverse patient reactions. Standardization of methods for determining the concentration and activity of such components should be considered by developers and manufacturers during the development and subsequent certification of these devices [110].

Quality control of biologically active plant-based substances differs significantly from the approaches applied to synthetic compounds. This is due to several specific challenges that complicate their standardization and control [69, 111, 112]. The main challenges include:

– complex mixture of components. Biologically active substances derived from plant material are often multi-component mixtures, making their chemical com-

position significantly more complex than synthetic substances. This complexity necessitates comprehensive analytical approaches for identifying and controlling all components [113];

– unknown active substances. In many cases, the specific substance or group of substances responsible for the therapeutic effect remains unknown. This complicates the creation of specifications based on active ingredients and requires the use of marker compounds or general phytochemical profiles for quality assessment [114, 115];

– lack of selective analytical methods and reference standards. For many plant-based components, particularly mixtures and extracts, selective analytical methods or reference compounds are not always available, complicating precise analyses. This necessitates method adaptation and, in many cases, the development of new approaches for component identification and quantification [112, 116];

– natural and chemical variability. Plant materials can exhibit significant natural variability in chemical composition depending on environmental factors such as climate, soil, and other conditions [117]. This creates additional difficulties in standardization, as ensuring complete uniformity in each batch is nearly impossible;

– existence of chemical varieties and cultivars. Plants may exist in different chemical varieties and cultivars with distinct chemical profiles. These varieties can significantly differ in active component content and thus require thorough identification and quality control [118];

– dependence of quality on raw materials and processing methods. The source, harvesting methods, drying, storage, transportation, and processing of plant material can significantly impact its final quality. For instance, extraction methods, solvent polarity, and component stability determine the final product's chemical composition and biological activity [119].

The influence of anthropogenic factors, such as environmental pollution and the use of modern biotechnologies, can lead to changes in the physicochemical properties of biologically active substances used in medical devices [120]. This underscores the need for strict standardization and control of these parameters to ensure patient safety.

These challenges require the development of specialized quality control approaches, including detailed standardization of processing procedures and the use of comprehensive analytical methods such as chromatography and spectroscopy to confirm the composition and stability of biologically active plant-based substances [112, 121].

In our opinion, the development of specifications for medical devices made from biologically active substances can be based on the same practices used for pharmaceuticals – applying the Pharmacopoeias of countries with stringent regulatory practices, as well as the standards of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which outline requirements for specification development, analytical control methods, and validation criteria for control methods, in addition to ISO standards. The 2021 guideline on the standardization of medical devices, MDCG 2021-5, even encourages the use of harmonized EMA standards [122]. In this case, each device made from plant-based components will be accompanied by a well-founded specification and a set of validated analytical tests.

A practical confirmation of the importance of standardizing physicochemical parameters to ensure the safety and efficacy of medical devices containing biologically active substances is the development of suppositories based on plant extracts for treating prostatitis. When creating such products, controlling parameters that determine product quality is crucial, including average mass, melting temperature, deformation and disintegration time, microbiological purity, and pH level [123].

One of the critical indicators is the identification of the structure and quantitative determination of potential degradation products of biologically active substances and the devices containing them. Determining possible degradation products (impurities) in pharmaceutical and medical products is crucial, as unidentified and potentially toxic impurities can pose a health risk to patients [124]. Due to the diverse chemical structures and properties of extracted and leached compounds, various analytical challenges arise during their identification and quantification [125].

Various analytical methods can be applied to obtain information about the structure of a biologically active substance and its degradation products [112, 119]. These include spectrometric methods (e.g., infrared (IR), near-infrared (NIR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)), chromatographic methods (e.g., high-performance liquid chromatography (HPLC), gas chromatography (GC), high-performance thin-layer chromatography (HPTLC)), and capillary electromigration methods (e.g., capillary electrophoresis (CE)) in combination with different detectors (e.g., LC-UV/Vis, which combines liquid chromatography (LC) for compound separation with spectrophotometry in the ultraviolet-visible (UV-Vis) range for detection and identification of compounds) [112]. The quality of the obtained information depends on the sample's preprocessing and the selected chemical methods [121].

To ensure accurate and efficient quality control of biologically active substances, various methods must meet requirements for accuracy, cost-effectiveness, and ease of application. HPTLC is a popular method widely used in pharmacopoeias [126]. However, this method may require significant reagent costs and highly qualified personnel. Therefore, alternative cost-saving approaches are becoming increasingly relevant for quality control laboratories [112].

One such method is attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), which can be used as a cost-effective alternative to HPTLC [127, 128]. This method has several advantages [128], including:

– minimal or no sample preparation, significantly reducing analysis time;

– reduced need for solvents and reagents, lowering operational costs;

– the ability to obtain rapid results while maintaining accuracy and reproducibility, thanks to the use of chemometrics for data analysis.

However, for the widespread use of ATR-FTIR, the availability of Botanical Reference Materials (BRM) is necessary, as they are essential for validating analytical methods [112]. In cases where BRM is unavailable, reference botanical or herbal materials must first undergo standardization, usually through liquid chromatography-high-resolution tandem mass spectrometry (LC-HR-MS/MS). This approach allows for precise determination of the biochemical composition of the substance, forming the basis for creating accurate BRM and subsequent application of ATR-FTIR for rapid assessment of plant raw material quality [129].

To establish quality criteria, it is advisable, during the development stages of a medical device based on a plant-derived biologically active substance, to start with a complex method for precise identification and degradation product analysis (e.g., LC-HR-MS/MS or NMR), and then transition to a relatively cost-effective method (e.g., ATR-FTIR, HPTLC, LC-UV/Vis) for routine quality control [128]. These studies may also include stress testing, which provides information on potential degradation products and product stability [130]. It is worth noting that a comprehensive study of a product's physicochemical properties can later provide valuable information for biological evaluation using the WoE approach [80].

5. Discussion

The study's most significant result is identifying the impact of new regulatory requirements (specifically, Regulation (EU) 2017/745) on the classification of medical devices containing biologically active substances. It has been established that the Regulation introduced specific classification rules (e.g., Rule 21), which take into account the route of administration and systemic absorption of substances and, unlike the previous Directive, exclude the possibility of assigning such devices to Class I [24]. This change is critical, as it now requires all similar devices to undergo assessment by a notified body, thereby increasing the level of oversight and patient safety.

The study also highlighted specific challenges in ensuring the biological safety of these devices, including the comprehensive assessment of biocompatibility, standardization of physicochemical characteristics, and risk management. It was found that the traditional approach (e.g., relying solely on ISO 10993 standards) may not account for all risk aspects. Therefore, it was proposed to adapt biocompatibility assessment methods by applying the "Weight of Evidence" (WoE) concept to integrate heterogeneous data and obtain more substantiated safety conclusions [80].

Another significant result is the presentation of specific examples differentiating medical devices from medicinal products based on their primary mode of action. It was demonstrated that even if substance-based devices have a similar dosage form and medical purpose as medicinal products (e.g., eye drops, creams, capsules), their classification depends on the non-pharmacological nature of the primary action (mechanical, barrier, physical, etc.), distinguishing them from pharmacological products [24].

As a result of the study, modern approaches to safety assessment of such devices were analyzed (including the implementation of systematic risk analysis and WoE), and their effectiveness in providing a more precise characterization of the safety profile of innovative medical devices was demonstrated. This underscores the necessity of a comprehensive approach, where each of the identified findings – from regulatory classification to testing methods – contributes to the overall biological safety of the device.

Practical relevance. The conducted research provides a comprehensive analytical framework for addressing the regulatory and scientific challenges associated with the classification and safety assessment of medical devices containing biologically active substances. Given the increased attention to such products under Regulation (EU) 2017/745 and the necessity to distinguish them from medicinal products, the proposed approaches offer practical value for developers, manufacturers, and regulatory experts.

Research limitations. Despite the comprehensive analysis, the study has a number of limitations. The classification and regulatory assessment of medical devices containing biologically active substances heavily depend on changing interpretations of European legislation. This creates uncertainty due to the dynamic nature of updates to the MDCG guidelines and the lack of clear experimental criteria to distinguish between non-pharmacological mechanisms of action. Several case studies have been included to illustrate the nuances of the classification; their regulatory interpretations may differ from jurisdiction to jurisdiction and should not be considered as universal precedents.

Prospects for further research. Further research should be aimed at developing scientifically based models for the functional assessment of complex multicomponent herbal formulations, which are currently difficult to classify within the existing regulatory framework. Interdisciplinary cooperation between regulatory experts, toxicologists, chemists and pharmacologists will be important to address the complex issues related to the regulation and safe use of medical devices containing biologically active substances, especially in the context of harmonisation of the regulatory frameworks of Ukraine and the EU.

6. Conclusions

The implementation of new approaches in the classification and safety assessment of medical devices containing biologically active substances contributes to a more accurate evaluation of risks and potential health impacts on patients. The analysis of current regulatory requirements, particularly ISO 10993 standards and the Regulation, allows for the adaptation of the WoE methodology for comprehensive biocompatibility assessment, which is crucial for devices with high structural and functional complexity. At the same time, the need to expand regulatory recommendations

regarding experimental validation of the mechanism of action of such devices remains an open issue. Such an approach could enhance confidence in the safety of medical devices and ensure the harmonization of their assessment with international standards.

The development and quality control of medical devices based on biologically active substances is a multifaceted process that includes component identification, degradation product analysis, and the standardization of research methods. Establishing clear quality criteria and applying modern analytical methods such as spectroscopy, chromatography, and other techniques contributes to increased reliability and reproducibility of results. These methods should be precise and economically justified, which is essential for routine quality control. Implementing alternative approaches, such as ATR-FTIR, improves control efficiency by providing fast and accurate results while reducing operational costs.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship, or other interests that could influence the study and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in creating the presented work.

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