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Substance-based medical devices made of natural substances: An opportunity for therapeutic innovation

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The approval of EU Regulation 2017/745 has created a regulatory framework capable of consolidating an entire category of therapeutic products, that of Substance-based Medical Devices. The Regulation creates the conditions required to promote innovation in therapeutics, both for the so-called "minor illnesses" as well as for important "unmet medical needs". At the same time, it significantly raises the standards for evaluating their efficacy and safety. Among the different kinds of Substance-based Medical Devices, those made of natural complex substances offer a special opportunity. In this new regulatory context, natural substances can be made available to the patient within an "evidence-based" context, guided by the principles of Systems Biology and Systems Medicine, and under the control of the healthcare sector. Substance-based Medical Devices are already an important product in the European therapeutic market and will likely play an increasing role in the years to come.

KEYWORDS

substance-based medical device, medical devices made of substances, natural substances, innovation, herbal medicines, medical device regulation, mechanism of action, therapeutic effect

Introduction

The therapeutic scenario appears in continuous evolution to catch up with changes in research and development, the environment, and standards of well-being worldwide. Meeting these demands is a continuous challenge, which should take advantage in basic and medical science, technology and big data management.

There are two areas where these changes are particularly interesting:

Abbreviations: EU, European Union; MAT, Moving Annual Total; MDR, Medical Device Regulation; MP, Medicinal Product; OTC, Over-the-Counter; SBMD, Substance-based Medical Device; THMP, Traditional Herbal Medicinal Product.

1- In improving the benefit/risk ratio of current therapeutics, with a aim of minimal impact on the physiology of the whole body, especially in the long term, and on the environment.
2- In managing the complexity of new diseases and treatments: degenerative, metabolic and functional diseases, as well as multifactorial syndromes, occur at an increasingly higher frequency as the population ages (Van den Berg et al., 2006, Kelishadi 2007, Cockerham et al., 2017, GBD 2015 Obesity Collaborators 2017, DeBoer 2019, Cobiac and Scarborough 2021, Dellafiore et al., 2022, Guarino et al., 2022 (review), Nguyen et al., 2022) and often have unsatisfactory or inadequate treatments (Black and Ford, 2021; Strisciuglio et al., 2021; Bousaba et al., 2022; Negi et al., 2022; Singh et al., 2022).

The global challenges also include the so-called "minor illnesses". Lack of adequate innovation over the past 50 years has limited the therapeutic options for both patients and health professionals, calling for the development of new therapeutic approaches and solutions. All these situations may be considered as "unmet medical needs" and they will likely impact the quality of life of patients and their caregivers. Thus, it is of the utmost importance to promote innovation in patient management, in particular by promoting therapeutic products with an increasingly favourable benefit/risk ratio, especially in populations such as children, adolescents and the fragile elderly.

In this context, the Medical Device Regulation (MDR), EU Regulation 2017/745, was developed and approved by the Council and the European Union (EU) Parliament. It regulates an emerging category of products known as Substance-based Medical Devices (SBMDs). These medical devices are similar to medicinal products (MPs) in terms of their therapeutic effect and pharmaceutical formulations. However, the main difference between the two categories is that medical devices are intended for the "investigation, replacement or modification of the anatomy or of a physiological or pathological process or state" (Article 2 (1) of Regulation 2017/745), while medicinal products are used with a view to "restoring, correcting or modifying physiological functions" (Article 1 (2) of EU Directive 2001/83, as amended). Consequently, they differ in their mechanism of action: MPs have a pharmacological mechanism (acting on a specific biological target, e.g., receptors, enzymes) (Capone et al., 2012; Racchi et al., 2016) and must be able to modify a function, while SBMDs have "any mechanism that is not pharmacological (interacting with a constituent of the human body at a multifactorial and non-targeted level), and must be able to modify a process or state" (Sardi et al., 2018; Greco et al., 2020; Racchi and Govoni, 2020).

The MDR's inclusion of different type of product has created a significant opportunity for innovation. The Regulation made it possible to repurpose the therapeutic properties of natural complex substances, which were unused, or even considered as complementary and alternative medicine, within an evidence-based framework and as part of the healthcare sector.

In 2001, this issue was addressed but remained unresolved, since it classified all these products as "Traditional Herbal Medicinal Products (THMPs)". According to Article 16 of Directive 2001/83, the mechanism of action of a THMP did not need to be described and these compounds were approved for sale on the basis of a "plausible efficacy and safety", supported only by their traditional use (i.e., use within the EU for at least 15 years and in the world for at least 30 years). Even in the few cases of (very old) products authorised on the basis of their "well-established use", whose clinical efficacy could be demonstrated by published studies, the quality and mechanism of action have always been referenced to a single marker or, at most, 2–3 markers. In fact, the therapeutic use of natural substances within drug legislation required the selection of a single marker within the complex substance, and the mechanism of action and the effect of the final product had to be associated with that specific single marker. Consequently, the medicinal product legislation is not adequate to assess the value of natural substances, particularly the emergent properties deriving from their complex composition. Nowadays, this "reductionist approach" has been revised by the same regulatory agencies, since it does not reflect the real mechanism of action and cannot be established according to the rigid requirements of drug development. The ultimate price for this view is a complete lack of innovation.

Regulation 2017/745 lays out the possibility of using complex natural products and relying on "evidence-based" data, classifying these substances as complex biological substances (General Safety and Performance Requirement 13.3, Annex I of MDR). This legitimises the new criteria required to demonstrate the mechanism of action, which rely on evidence generated through Systems Biology. Through advanced techniques, it is now possible to characterize and standardize the complex mixture contained within natural products "as a whole system", without limiting its characterization to a single selected marker. This is a crucial improvement, since the standardization of a single marker cannot guarantee reproducibility between different batches of the product and, ultimately, cannot ensure the reproducibility of the benefit-risk ratio demonstrated in clinical studies. The therapeutic opportunity of SBMDs is widely confirmed by market data, which show an increasing use by patients and health professionals, and by the growing number of published clinical studies.

Substance-based medical devices: Market share

Market data can help us understand the importance of this sector both for the industry and patients.

TABLE 1 Summary of sales data showing the importance of SBMDs in the total self-medication sector, including food supplements, in some European Union Member States.

Market	Italy	Poland	Spain	France	Germany*
SBMD Market value (million €)	1,153 €	301 €	307 €	447 €	956 €
SBMD market units (million)	86	60	26	64	68
SBMD Market share value of self-medication	15.2%	9.5%	11.5%	7.0%	9.6%
SBMD value market Trend (MAT April 2022 vs. MAT April 2021)	+20%	+32%	+24%	+20%	+11%
Total Self-medication value market Trend (MAT April 2022 vs. MAT April 2021)	+13%	+21%	+19%	+10%	+13%
SBMD number of products on the market in April 2022 (launched on the market since 2016)	3,689 (1,994)	1,594 (876)	686 (415)	734 (375)	2,469 (1,239)
SBMD average price (self-medication average price)	13.33 € (12.50 €)	4.97 € (3.98 €)	11.87 € (9.44 €)	7.00 € (4.64 €)	14.09 € (10.53 €)

Source: IQVIA, Sell Out Multichannel Self-Medication Market MAT, April 2022 (* Germany MAT, May 2022).

The above data concern five reference EU countries: Italy, Spain, France, Poland, and Germany. In particular, the data regarding Italy, Germany and Poland come from data enquiries conducted on the database of the main pharmaceutical data company (IQVIA), while those regarding Spain and France come from a partial reconstruction. For these two countries the entire market of nasal saline solutions, artificial tears and eye lubricants was considered, plus individual known SBMDs (Table1).

Aggregate data for these five markets indicate that the SBMD sector is worth 3.2 billion euros, equivalent to 304 million units (MAT May 2022 for Germany, MAT April 2022 for the other countries), and has grown +18% vs. +13.5% of the total self-medication sector (including OTC drugs, medical devices, food supplements and homeopathic medicines). The number of products registered as SBMDs is greater than 9,100, of which about 4,900 have been placed on the market since 2016. This means that the companies involved in the self-medication sector are investing a lot in the development of SBMDs. This is due to the degree of innovation being delivered by these non-pharmacologically acting products as well as the approval of Regulation 2017/745, which has clarified the EU regulatory framework. SBMDs currently represent 11% of the total self-medication market, with an average price of € 10.41 vs. € 7.47 for the total self-medication sector.

Looking more specifically at the Italian market, since Italy is a European benchmark in the SBMD industry, the product category is rapidly changing the self-medication sector. As of April 2022, there are over 650 operating companies in Italy, for a market with a Moving Annual Total (MAT) in April 2022 of 1.1 billion € in value terms (31% of market share), and 87 million units in volume terms (25% of market share). The number of products classified as SBMDs has trebled since 2010, from 1,200 to 3,689 as of MAT April 2022. Of these, 1,994 products were placed on the market since 2016. Looking at the timeline, the SBMD sector is constantly growing. Notably, in 2010 it was worth € 331 million (12% of market share) almost trebling its market share. This means that three out of 10 self-medication therapeutic products sold are SBMDs. Since 2010, the growth of the self-medication sector has substantially relied on SBMDs. Interestingly, the average price of a SBMD is € 13.33, while that of the Over the Counter (OTC) medicinal products is € 12.50, implying that Patients, Medical Doctors and Pharmacists take into account the recent improvements and innovation of SBMDs and their positive benefit/risk ratio. All major multinational companies have extended their therapeutic offer through SBMDs.

In some cases, such as gastrointestinal conditions, SBMDs have grown to almost the level of OTC medicinal products: the Medical Device market share rose from 9% to 48% in sales value from 2010 to 2022. The cough market follows the same trend, increasing from a 7% market share in value in 2010 to a 24% share in 2022, especially in the pediatric population. While in 2010 the first SBMD cough syrup sold in Italy was the sixth best-selling product (Source: IQVIA Flexview Multichannel Italia - MKT Moving Annual Total Apr 2022), in 2022 it became the first. The same situation is reflected in Spain and Portugal, with a cumulative annual sales volume between the three countries of five million units.

It is evident that SBMDs are a central asset to the EU health system, and their development has made it possible to find beneficial treatments for common disturbances, addressing common and largely unmet medical needs.

Within this context, a special role is played by SBMDs made of natural substances. In Italy, as of MAT April 2022, SBMDs containing at least one natural complex substance (not an isolated molecule of natural origin but a complex matrix of plant raw materials) is approximately 50% of both the volume and value of the total SBMD market, while in 2010 it was 38% of its value and 42% of its volume, as shown in Figure 1.

Since it is not possible to describe the mechanism of action of complex substances within the regulatory framework defined by Annex I of Directive 2001/83 (as amended), the possibility of registering complex natural substances as innovative drugs is only theoretical and all new products will necessarily be

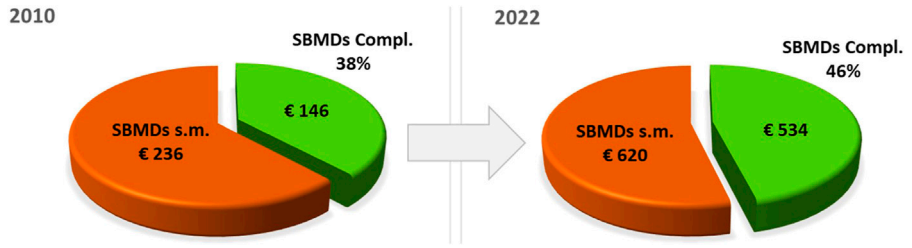

FIGURE 1
Market share of SBMDs made of natural complex substances. In Italy, the sector was worth € 146 million (38% of market share of the SBMD market) in 2010 and grew to € 534 million (46% of market share of the SBMD market) in 2022 **(A)**. Market SBMDs s.m. + SBMDs compl MAT SEPT 2010. Sell out € 382 million equal to 34 million pieces. **(B)**. Market SBMDs s.m. + SBMDs Compl. MAT APR 2022. Sell out € 1,154 billion equal to 86 million pieces. Source: IQVIA Sell Out Multichannel Market SBMD s.m. + SBMD Compl.—Sell out value (€ million) MAT SEPT 2010—MAT April 2022. SBMD s.m., SBMD made of single molecules; SBMD Compl., SBMD containing at least one natural complex component.

registered as Traditional Herbal Medicines. This problem can only exacerbate the lack of innovation in herbals containing complex substances, even in a country such as Germany whose industrial system has all the potential to perform important research and innovation in this field.

The MDR establishes a regulatory framework which allows innovation while meeting strict quality, safety and efficacy requirements and is also becoming a benchmark outside the EU. Regulations developed in Australia, Saudi Arabia, the United Arab Emirates, Morocco, Israel, Argentina, Turkey, Cuba, and Switzerland, to name but a few, have taken the EU system as their model.

Substance-based medical devices: Special provisions and global access to the market

The MDR provides SBMDs with special provisions to guarantee that only products with the highest safety and efficacy standards are marketed. In particular, the pre-marketing clinical evidence necessary to demonstrate the benefit/risk profile of devices has been significantly strengthened. All post-market surveillance and vigilance activities have likewise been improved, establishing a regulatory context which compels the manufacturer to perform a continuous and active evaluation of its products. The evaluation of clinical data, post-market surveillance and vigilance activities are not only necessary for patient safety but are also opportunities for innovation and research. The possibility of conducting interventional, comparative, often randomized clinical studies which evaluate new products versus the current standard of care, as well as the implementation of Real-World Evidence, are extraordinary and novel forces driving research and innovation.

With respect to Directive 92/43 (as amended), the MDR introduced a new classification rule, Rule 21. This rule does not include all SBMDs (for example injectables are excluded) but it regulates the SBMDs "*that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body*".

This rule significantly increases the standards required to obtain the certification of these medical devices. For example, compared to Directive 93/42, it eliminates the possibility of classifying devices in class I (which requires only a simple self-certification by the Manufacturer). This evolution is desirable, since in some cases, low quality devices or devices with no added value to the current standard of care are marketed. According to Rule 21, all SBMDs need to be evaluated by a Notified Body to guarantee efficacy, safety, and a sound benefit/risk profile.

It is worth mentioning that the first indent of Rule 21 introduces an important change into the framework of Directive 93/42: it envisages the possibility of CE marking products which should be systemically absorbed in order to achieve their intended use as SBMDs. This is a category of product that was not included in Directive 93/42 and it opens important avenues for innovation, in particular for the use of natural substances in the treatment of "systemic" disturbances such as insomnia, urinary tract infections and so on. The Regulation stipulates that these types of SBMD should be classified into the highest risk class (class III) and that a drug agency of a Member State be involved in the assessment, in addition to the Notified Body.

During the legislative process to approve the MDR, as well as during the Trilogue phase, the EU Parliament has strongly defended the entire SBMD category to encourage their development, innovation, and research. The initial MDR proposal has been extensively discussed and finally approved after 5 years. The final agreement achieved an important political compromise, offering a great opportunity to invest and develop new research trends for sustainable health.

Discussion

The new medical device Regulation provides a framework that opens up innovative treatments and ensures a positive benefit/risk profile for the products under its jurisdiction. Within the SBMD sector, there has been a particular focus on the possibility of developing new therapeutic products made of natural complex substances.

The market data, the rapid development of the scientific literature and clinical studies clearly indicate the importance and innovative value that this category of products has to offer to the European health, social and economic sectors. The demand for these products from patients and professional health care providers, including physicians, indicates that they can satisfy health needs, with a positive impact on the population's quality of life. The market data show that SBMDs are not in competition with medicinal products, but rather play a role in extending the therapeutic armamentarium with new treatment possibilities, thus broadening patients' choice.

In the sector of natural complex substances, Regulation 2017/745 opens up extraordinary opportunities for development of innovative, efficacious natural products, whose safety is important for both humans and the environment. Indeed, natural products are biodegradable due to their natural origin (EMEA/CHMP/SWP/4447/00 corr 2 2006; EMEA/CHMP/SWP/4447/00 rev.1 2018), a relevant aspect which is in line with the political, economic, and social strategies defined by the "Next Generation EU" program.

Having provided a clear regulatory framework, SBMDs, whether natural or synthetic, can be developed as safe, effective, and innovative therapeutic products, and it is necessary to implement the Regulation correctly, in order to respect the intentions of the legislator.

This involves a variety of tasks for stakeholders and Regulatory bodies:

- Industry's task is to adapt its skills to the new requirements, and to align with the challenge of increasingly innovative product development.
- The Research and Development sector's task is to continuously generate robust evidence that proves the efficacy and safety of these products. The generation of new data and the development of more specific methods of clinical evaluation to demonstrate the efficacy and safety of natural complex therapeutic products are of particular importance, to provide a sound and adequate evaluation of risks and benefits as required by Regulation 2017/745 on SBMDs.
- The task of the Regulatory bodies is to effectively implement the Regulation. This means an end to the restrictive attitude that systematically classifies any product with a therapeutic activity as a medicinal product regulated according to the Directive 2001/83 Article 2 (2). On the contrary, medical device and medicinal product legislation should be developed as two coordinated systems that jointly aim to guarantee the widest spectrum of treatment choices and safety for the patient. More specifically, pharmaceutical legislation can continue to be the normative frame of reference for cases in which the therapeutic activity is entirely and exclusively ascribable to a specific molecule contained within it, while the SBMD framework should be taken as the reference when the action is linked to the emergent properties of the entire complex natural system. In the former case, in fact, the mechanism of action can be developed within a pharmacological context (up to the purification of the active molecule), while the latter remains within an evidence-based framework but one that is oriented to the principles of Systems Biology.

Failure to do so would result in harm to EU patients, since it is known that the characteristics of these products, which are intended to have a therapeutic effect by targeting "a physiological process or state" through a "non-pharmacological" mechanism of action, could no longer be registered as drugs. It is therefore not a question of whether these products should be classified as drugs or devices, but whether we want to support or prevent the development of effective and safe new treatments for humans and the environment. If this developmental roadmap is followed, it will create opportunities for everyone; if it fails, these products will be narrowed and limited to the realm of alternative medicine, with major safety and social consequences.

We are witnessing the rise of new types of products, new research patterns, and a significant expansion in the therapeutic tools that are accessible to all, and for the benefit of all.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions. We carried out queries against payment on a professional data set (IQVIA), cited when necessary, especially on each caption. Requests to access these datasets should be directed to Sofia Musella, smusella@aboca.it; Enrico Novelli, enovelli@aboca.

Author contributions

EG conceived and wrote the manuscript.

Conflict of interest

Author EG is a member of Confindustria Substance-based Medical Device Group and is employed by Aboca S.p.A.

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