

# Analysis of Medical Device Alerts Issued by the Portuguese Medicines Agency: Scoping the Purpose of New Regulatory Recommendations



## Análise dos Alertas Sobre os Dispositivos Médicos Emitidos pela Agência Portuguesa do Medicamento: Delineando o Propósito de Novas Recomendações Regulatórias

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### ABSTRACT

**Introduction:** Medical devices are healthcare technologies with a significantly growing market worldwide. This study aims to analyze medical device alerts issued by the Portuguese Medicines Agency, INFARMED, I.P. during 2017, as well as to identify the respective regulatory actions and to suggest additional recommendations.

**Material and Methods:** All alerts on medical device alerts publicly available in the website of INFARMED, I.P. were identified and analyzed, including actions taken. Additionally, reports on medical devices from the Portuguese national competent authorities were compared with reports from other European Union member states such as Germany.

**Results:** A total of 32 safety alerts were identified: 18 (56%) related with devices without identified records of commercialization in Portugal, six (19%) related with devices voluntarily withdrawn from the market, such as counterfeit products, and eight (25%) categorized as 'other'. In both Portugal and Germany, 0.28 and 4.53 reports of national competent authorities per million inhabitants were identified, respectively. Diverse regulatory actions were taken, such as six compulsory indications to not acquire or use devices.

**Discussion:** Considering that the European Union is an open market where citizens should have equal access to medical devices, the Portuguese system of medical device safety alerts seems to be functioning normally. The identified safety alerts seemed relevant, with Portugal registering a proportionally slightly lower number of alerts when compared with higher sales volume markets, which may be explained by an underreporting of this type of problems. Further studies are needed to confirm these preliminary results, although the development of databases comprising data on patients using medical devices is recommended in order to generate automatic email and text message alerts.

**Conclusion:** A limited number of safety alerts on medical devices was identified in Portugal, with few reported cases of counterfeit or falsified devices. The Portuguese Medicines Agency contributes to the citizens' access to quality medical devices, by issuing safety alerts, recommendations and mandatory market withdrawals for unsuitable or unsafe medical devices.

**Keywords:** Equipment and Supplies; Patient Safety/legislation & jurisprudence

### RESUMO

**Introdução:** Os dispositivos médicos são tecnologias de saúde com um significativo crescimento a nível mundial. Foi objetivo deste trabalho analisar os alertas sobre dispositivos médicos emitidos pela Agência Portuguesa do Medicamento: INFARMED, I.P. durante 2017, identificar as respetivas ações regulatórias e sugerir recomendações.

**Material e Métodos:** Todos os alertas e ações sobre dispositivos médicos publicamente disponíveis no website do INFARMED, I.P. foram identificados e analisados. Adicionalmente, os relatórios da autoridade competente nacional sobre dispositivos médicos foram comparados com relatórios de outros países da União Europeia como a Alemanha.

**Resultados:** Identificou-se um total de 32 alertas de segurança de dispositivos médicos: 18 (56%) sem registos de comercialização em Portugal, seis (19%) voluntariamente retirados do mercado, como produtos contrafeitos, e oito (25%) categorizados como 'outros'. Em Portugal e na Alemanha foram identificados 0,28 e 4,53 relatórios de autoridades competentes por milhão de habitantes, respetivamente. Diversas ações regulamentares foram tomadas, como seis indicações obrigatórias para não adquirir ou utilizar dispositivos médicos.

**Discussão:** Considerando que a União Europeia é um mercado aberto no qual os cidadãos detêm igual acesso à utilização de dispositivos médicos, o sistema Português de alertas de segurança sobre estes dispositivos parece ter uma atividade normal. Os alertas de segurança identificados aparentam ser relevantes, com Portugal a registar um número ligeiramente inferior de alertas quando proporcionalmente comparado com outros mercados de maior volume de vendas, o que eventualmente pode ser explicado por uma subnotificação deste tipo de problemas. São necessários estudos adicionais para confirmar estes resultados preliminares, sendo o desenvolvimento de bases de dados sobre o uso de dispositivos médicos pelos doentes recomendado de forma a gerar emails e alertas telefónicos automáticos.

**Conclusão:** Foi identificado um número limitado de alertas de segurança em dispositivos médicos em Portugal, com escassas notificações de contrafação ou falsificação. A Agência Portuguesa de Medicamentos contribui para o acesso dos cidadãos a dispositivos médicos de qualidade, através da emissão de alertas de segurança, recomendações e retirada obrigatória de dispositivos médicos

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inadequados ou inseguros do mercado.

**Palavras-chave:** Equipamentos e Suprimentos; Segurança do Doente/legislação & jurisprudência

## INTRODUCTION

The Portuguese Law-Decree 145/2009 is based on the corresponding European Union (EU) directive 93/42/EEC.<sup>1</sup> This Law-Decree defines a medical device (MD) as “any instrument, apparatus, appliance, equipment, material or another article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer, to be used for human beings for the purpose of diagnosing, preventing, controlling, treating or attenuating a disease; diagnosing, controlling, treating, attenuating or compensating for a lesion or a deficiency; studying, substituting or altering the anatomy of one physiologic process; and birth control.”

MDs are classified as (i) MDs of class I or low-risk devices (e.g., diapers, incontinence pads, elastic stockings, walking aids, etc.); (ii) MDs with a medium risk belong to classes IIa (e.g., hydrophilic gauze, urinary catheters, syringes, etc.) or IIb (e.g., insulin pens, diaphragms, contact lenses), with a likely higher risk in IIb when compared with IIa; and (iii) MDs of class III or MDs of high risk (e.g., condoms with spermicides, intrauterine device that does not release progestogens, etc.). This classification is based on risk criteria, such as the time, degree or location of contact between a MD and the human body, since some MDs are more invasive than others or are meant for chronic use.<sup>2</sup> Considering the regulation 2017/746 of the European Parliament and of the Council of the 5<sup>th</sup> April 2017 on *in vitro* diagnostic medical devices (preliminary point 10): “all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are *in vitro* diagnostic MDs”.<sup>3</sup>

Additionally, MDs must have a *conformité européenne* (CE) mark, which is a conformity sign proving the device is compliant with the relevant directives. Devices with this mark may be marketed in any EU country.<sup>1,4</sup> The conformity assessment procedures of MDs may be carried out under the responsibility of the manufacturers for Class I devices (general rule). Class IIa devices require the intervention of a notified body (NB), i.e. bodies responsible for the conformity assessment of MDs after production. NBs are designated by the EU member states and each member state shall notify the Commission, as well as the remaining member states about the designated bodies. NBs may ask the manufacturer for information or data for establishing/maintaining the attestation of conformity of MDs. Classes IIb and III necessarily require the inspection by a NB concerning the design and manufacture of MDs. Class III products explicitly require prior authorization regarding conformity before being placed on the market.<sup>1</sup>

In the EU, the market of MDs comprises around 27 000 companies: 95% small and medium-sized enterprises, with great innovation efforts: on average, a new patent is issued

every 40 minutes and the product lifecycle is approximately of 18 months. These companies employ over 675 000 workers, participating in a growing market (over €110 billion). The key trend of MD industries on cost efficiency is based on the compulsory creation of value for payers and patients, which is intended to ensure that users of MDs benefit in terms of the product's efficacy, safety, efficiency, and cost. For instance, Australian importers are specifically oriented to acquire cost-effective MDs, which can improve patient health outcomes and reduce healthcare costs due to the increasing number of an aging population.<sup>5</sup>

The regulations on MDs cover diverse aspects of product development and vigilance systems, from design to manufacture, clinical testing, authorization and post-market surveillance.<sup>6</sup> Although post-marketing surveillance is essential in the detection of non-conformities, quality issues, adverse events, or the presence of falsified devices in the market,<sup>7,8</sup> a specific post-market surveillance system for medical devices was only defined through a recent/new European Commission regulation (EC 2017/745) on medical devices in the EU (Chapter VII).<sup>9</sup> The 520/2012 EC Regulation established a specific pharmacovigilance system for medicinal products,<sup>10</sup> although a previous Council Directive (93/42/EEC) stated that the protection of health and the associated controls should be more effective by means of medical device vigilance systems, integrated at Community level.<sup>1,9</sup> In this sense, the European Database on Medical Devices (EUDAMED) is the information system for exchanging legal information related to the application of EU Directives on MDs.<sup>7,11,12</sup>

According to the publicly available information of the EU, the overall number of registered adverse MD events has been stable for the last five years, despite the constant market growth.<sup>12</sup>

In Portugal, it the following notifications of incidents and safety corrective actions related to MDs are reported in the official medicines statistics from INFARMED, I.P. (n = MDs registered/notified until the end of the year): 1542 (n = 199 823) in 2014, 1479 (n = 207 443) in 2015, 1790 (n = 226 948) in 2016, 1645 (n = 244 138) in 2017 and 1741 (n = 277 834) in 2018.<sup>13</sup>

Considering the NCAR (National Competent Authorities Reports) from 17 EU countries, a total of 981 relevant events with MDs were notified in 2017.<sup>7,12</sup> NCARs are “intended for dissemination between National Competent Authorities and the Commission”; their qualitative information is not public. NCAR should be created in accordance with a regulated form/template: “This form should be completed by NCAR participants only when exchanging safety information about relevant measures and/or recommendations relating with the prevention of adverse incidents concerning medical devices. This form is designed for exchanging information between NCAR participants; it should not be passed directly

on to patients, users, third persons or the public.”. Among the examples of incidents and field safety corrective actions which the manufacturer should report are “patient dies after the use of a defibrillator and there is an indication of a problem with the defibrillator”, “loss of sensing after a pacemaker has reached end of life; elective replacement indicator did not show up in due time, although it should have according to device specification” or “an infusion pump stops, due to a malfunction of the pump, but fails to give an appropriate alarm; there is no patient injury”, i.e. severe (or potentially severe) incidents with MDs.<sup>14</sup> In 2017, Germany (population = 82 521 653 inhabitants), United Kingdom (population = 65 884 142 inhabitants), and France (population = 66 809 816 inhabitants) had the highest prevalence of such serious incidents (981 (100%) NCARS exchanged between 17 Countries): 363 NCARs (37.0%), 190 NCARs (19.3%), and 115 NCARs (11.7%), respectively, while only 3 NCARs (0.3%) such incidents were specifically reported in Portugal (population = 10 309 573 inhabitants). As for countries with a similar population size to Portugal, 2017 data (981 (100%) NCARs exchanged between 17 countries), the number of NCARs and inhabitants: Czech Republic 4 NCARs (0.4%) (population = 10 578 820 inhabitants), Austria four NCARs (0.4%) (population = 8 772 865 inhabitants), Belgium 40 NCARs (4.1%) (population = 11 351 727 inhabitants) and Sweden 44 (4.1%) NCARs (4.5%) (population = 9 995 153 inhabitants).<sup>7,12,15</sup>

Besides registering incidents with MDs, national medicines agencies (one in each EU country) are responsible for other functions, namely designation of MDs, inspection of manufacturers or MDs, including the collection of MDs samples, proceedings of infringement (e.g. application of fines) or implementing and monitoring the implementation of national and international regulations on MDs, including the publication of MD safety alerts.<sup>1</sup> These are directed to healthcare professionals and patients.<sup>16</sup>

Given that MDs may be associated with severe or potential severe incidents/events and patients may under-use safety information on MDs,<sup>7, 12-14</sup> the aims of this study were: (i) to identify and categorize all alerts on MDs issued by the Portuguese Medicines Agency, INFARMED, I.P. during 2017 and published in its official website, (ii) to compare the occurrence of Portuguese safety alerts with the rates in other EU countries and, (iii) to discuss measures to mitigate the risks associated with safety concerns on MDs, i.e., to discuss possible new regulatory safety recommendations, which may be globally accepted, knowing medicines agencies and health authorities have a collaborative framework towards public health safety.

## MATERIAL AND METHODS

Descriptive study: safety alerts on MDs were collected through the web address of the Portuguese medicines agency (INFARMED, I.P.): <http://www.INFARMED.pt/web/INFARMED/alertas/dispositivos-medicos> during January 2018. These alerts also cover incidents with MDs marketed in the remaining EU countries. Thus, it is possible to obtain

an indirect indicator of all significant incidents with MDs in the EU.

## Inclusion and exclusion criteria

All Portuguese national safety alerts on MDs published by INFARMED, I.P. on the official website in 2017 (inclusion criteria) were analyzed because it was the most recently available information when the present study was carried out. Exclusion criteria: publications describing other types of safety issues.

## Portuguese safety alerts on MDs

Study data were extracted and processed as follows: (i) firstly, safety alerts were identified i.e. all safety alerts on MDs published in the official site of INFARMED, I.P. between January 1<sup>st</sup> 2017 and December 31<sup>st</sup> 2017, (ii) secondly, they were registered i.e. all online available information was collected in a word document and the original information was archived in digital format; and (iii) thirdly, these safety alerts were analyzed as follows: type of required action taken by the national competent authority (NCA) (devices that are voluntarily withdrawn from the market *versus* ‘other situations’) or identification of MDs marketed in Portugal *versus* MDs not marketed in Portugal. In the group of devices voluntarily withdrawn from the market, counterfeit or falsified devices were also quantified. The ‘other situations’ were based on qualitative classifications attributed by the researchers after reading the full content of each identified safety alert (please see ‘Portuguese safety alerts on MDs’ in the section of results). The present analysis was double-checked by two researchers.

Study variables were conveniently selected based on the publicly available information in the safety alert (published alert). Other variables were not available in these published safety alerts (e.g. the severity of a possible incident, class of device, possible year of commercialization in Portugal, the existence of Field Safety Actions).

## Actions taken by the regulatory authority

The actions taken by INFARMED, I.P. are presented in Table 1.

## Estimated proportions of NCARs per million of inhabitants

A sub-analysis about NCARs was carried out because it seems these reports are related with severe or potentially severe safety events.<sup>7,12-14</sup> Besides Portugal, the selected countries for this comparison were Germany, United Kingdom and France because they are considered leading European economies with a much larger population and MDs market than Portugal, thus potentially appropriate to detect emerging safety issues. Moreover, the Czech Republic, Austria, Belgium and Sweden were evaluated, since they present a similar population size to Portugal.<sup>15,17</sup>

According to the official reports, the number of NCARs sent by each country were Portugal (n = 3), Czechia (n = 4), Austria (n = 7), Belgium (n = 40), Sweden (n = 44),

**Table 1** – Actions taken by the Portuguese national medicines agency after a safety alert on MDs (n = 32; 100% safety alerts)\*

Type of action	Description	
Recommendations $n_1 = 26$ (81.2%)	<ul style="list-style-type: none"> <li>- contacting the retail seller to receive a new safety alert 6.3% (2 in 32)</li> <li>- contacting the distributors to receive a software update 9.3% (3 in 32)</li> <li>- recommendations to not purchase or use a certain MD, concerning MDs without records of commercialization in Portugal 56.3% (18 in 32)</li> <li>- using the MD according to the instructions 9.3% (3 in 32)</li> </ul>	
Mandatory Decisions $n_2 = 6$ (1.8%)	- immediately suspend commercialization and return all devices to the manufacturer and not acquire or use the MD 18.8% (6 in 32)	
<b>Total (<math>n_1 + n_2</math>)</b>		<b>32 (100%)</b>

\* The same MD can issue different safety alerts simultaneously

Germany (n = 363), United Kingdom (n = 190), and France (n = 115).<sup>12</sup>

The number of NCARs per million inhabitants in each of the evaluated countries was calculated considering: (i) the data of European 2011 census and the demographic data of Eurostat (2017 data) and (ii) the data of 2017 NCAR; please see the public reports here: [https://ec.europa.eu/health/md\\_sector/market-surveillance-and-vigilance\\_en](https://ec.europa.eu/health/md_sector/market-surveillance-and-vigilance_en).<sup>12,15,17</sup>

## RESULTS

### Portuguese safety alerts on MDs

A total of 32 (100%) safety alerts on MDs were identified in the official website of INFARMED, I.P.. Overall, 18 out of 32 (56%) devices without records of commercialization at a national level; eight out of 32 (25%) other situations and six out of 32 (19%) devices voluntarily withdrawn from the market (Table 1).

### Actions taken by the regulatory authority

The main actions taken by INFARMED, I.P. are presented in Table 1.

Regarding, the devices without records of commercialization at a national level (18 in 32), INFARMED, I.P. has recommended not to purchase or use the MD. These alerts were disseminated by NCAs from the United Kingdom, Germany, Denmark, and Poland. Particularly, one alert from the 18 alerts without records of commercialization at national level was about in vitro diagnostic medical devices: a CE marking was not affixed in reagents for in vitro diagnostics (these reagents were withdrawn from the market by the German authorities). Due the free movement of goods in the European Union, INFARMED, I.P. has specifically recommended that these reagents should not be purchased or used since, there is no evidence of their safety, quality or performance.

The 'other situations' (eight alerts) concerned limitations on the functioning of the MDs (e.g., software or instruction updates to overcome function issues, such as the limited capacity of a battery; suspension of commercialization and return of all devices to the manufacturer; or new instructions due to a quality issue). The cases of counterfeit or falsified devices are included in the group of alerts from devices voluntarily withdrawn from the market (six alerts).

### Estimated proportions of NCARs per million of inhabitants

Overall, at least three out of 32 MDs safety alerts were related to serious incidents, which is in line with the three NCARs notified in Portugal during 2017.<sup>12</sup> A rate of 0.28 NCARs (i.e. reports of relevant incidents, such as severe or potentially severe incidents) per million inhabitants in Portugal was calculated using 2011 census data and/or of 0.29 NCARs per million inhabitants using 2017 Eurostat data.<sup>12,15,17</sup> The EU countries with the highest proportion of NCARs were: Germany with 4.53 NCARs per million inhabitants, UK with 3.0 NCARs per million inhabitants, and France with 1.77 NCARs per million inhabitants. Regarding the countries with a similar number of inhabitants (population size) to Portugal: Czech Republic with 0.38 NCARs per million inhabitants; Austria with 0.46 NCARs per million inhabitants; Belgium with 3.52 NCARs per million inhabitants and Sweden with 4.40 NCARs per million inhabitants.<sup>7,12,15</sup>

The German, French, UK and Portuguese markets accounted for 26; 14.5; 9.8 and 1.2 billion euros in sales of MDs, respectively (2015 data).<sup>18,19</sup> Regarding exports and imports respectively of MDs (2017 data), the studied countries accounted for: German (25 811 and 16 676 million of euros), France (6984 and 9785 million of euros), United Kingdom (5513 and 7334 million of euros), Czechia (1053 and 974 million of euros), Austria (1909 and 1930 million of euros), Belgium (12 071 and 9689 million of euros) and Sweden (1441 and 1595 million of euros).<sup>20</sup>

## DISCUSSION

Overall, the number of public alerts on MDs in the official website of INFARMED, I.P. (32 safety alerts in 2017) is clearly below the total number of notifications of incidents and safety corrective actions concerning MDs in Portugal (n = 1645 out of 244 138 registered MDs in 2017).<sup>13</sup> In this sense, it is likely that INFARMED, I.P. has specifically published these alerts based on safety and potential risk criteria. For instance, the medicines agencies of the USA and Australia [Food and Drug Administration (FDA) and the Therapeutics Goods Administration (TGA), respectively] have also only published 11 and around 20 safety communications about MDs, respectively (2017 publications),<sup>21,22</sup> which seems to be aligned with the number of safety alerts on MDs published by INFARMED, I.P.. It seems MDs industry is safely operating, considering the limited number of

safety alerts published on the websites of medicines agencies, such as INFARMED, I.P., FDA and TGA.<sup>21,22</sup> However, more studies on the present topic are recommended. On the other hand, 981 NCARS were exchanged between 17 EU Countries during 2017,<sup>12</sup> although these NCARs may be about the same type of MDs.

### Portuguese safety alerts on MDs and actions taken by the regulatory authority

Concerning the 32 safety alerts identified in the official website of INFARMED, I.P., more than half of these alerts were related with devices without identified records of commercialization at a national level. This can be considered very encouraging regarding the dissemination of safety information, since people and products can circulate within the EU and citizens living in Portugal may be using an MD not marketed in this territory. Alternatively, it may be an indicator of lower usage of MDs within the Portuguese population due to a more limited budget (i.e. economic restrictions), enforcement of narrow criteria to select/buy MDs at hospital level or different population health needs. Interestingly, only one alert about an *in vitro* MDs not marketed in Portugal was detected. This may reflect the lower proportion of *in vitro* MDs in relation to the global number of marketed MDs. For instance, the total healthcare expenditure in Europe is as follows: 76.9% inpatient & outpatient care, other; 15.9% pharmaceuticals & other medical non-durables and 7.2% medical technology (6.5% medical devices, including imaging and 0.7% *in vitro* diagnostics) (2017 data).<sup>20</sup>

The types of actions taken by the national medicines agency (recommendations or mandatory decisions) were dependent on the severity of the alert. This was the case for the six mandatory decisions related with quality issues, e.g., counterfeit devices receiving market suspension and recall of default MDs, which were involved in the three incidents. Relevant information is lacking on the alerts of studied MDs, such as the severity of a possible incident, class of a device, possible year of commercialization, the existence of field safety actions, etc. These could be related with confidentiality issues and/or the information format. National medicines agencies are legally required to present this information in a structured way (NCAR), and some regulatory information should remain confidential (see Annex VII of MEDDEV 2.12/1 rev.8).<sup>14</sup>

Aside from the alerts on the EU websites, national medicines agencies and the compulsory MDs incident reporting system (Eudamed),<sup>12</sup> computer-based systems integrated into MDs or in apps for patients may contribute to increase the safe use of MDs. For instance, electronic means (e.g., automated emails), or software platforms, which are based on individual data and suitable algorithms and are programmed to simulate the use of MDs. Other applications are currently under development to assist the selection of the safest device for a certain patient.<sup>23,24</sup>

Actions to increase the awareness of healthcare professionals and patients are also needed. Moreover, differences in the proportions of notified safety alerts between countries

could be justifiable by a potential underreporting of cases, although there is no data to confirm this assumption. Users of MDs should be motivated to provide active feedback on how to improve MDs and how to anticipate possible incidents. Even though end-users are theoretically unable to acquire MDs (at least from the high-risk categories), since these MDs are acquired/purchased by hospitals, patients should remain informed on the content of MDs alerts, especially if consumers carry one MDs inside the body (or directly contacting with the body). Only MDs coded by INFARMED, I.P. and included in the respective database may be purchased by the National Health Service (SNS) in Portugal.<sup>25</sup> In this sense, a unique ID code for each MD in the EU market would be an important step to ensure traceability and to establish causality in both positive and negative patient outcomes.<sup>26</sup>

### Estimated proportions of NCARs per million of inhabitants

The estimated proportion of NCARs per million inhabitants in Portugal is below the values registered by the other evaluated EU counterparts, including the analyzed countries with similar population sizes to Portugal (i.e. Czech Republic, Austria, Belgium and Sweden).<sup>12</sup> This situation may be explained by the fact that Portugal and the Czech Republic are among the countries with the lowest number of sales of MDs, thus being more likely to present a small number of NCARs per million inhabitants.<sup>15,18-20</sup> Additionally, this seems to be a low proportion of reports looking at the German market, which is approximately 23 times more valuable than the Portuguese one; however, Germany registered a rate of MD safety alerts only 16 times higher than Portugal.<sup>18-20</sup> Finally, at least some MDs safety problems may not have been notified by users/patients or healthcare professionals (i.e., underreporting of safety problems of MDs) and the number of inspections to identify falsified or unsafe MDs may be limited in our country. In this sense, vigilance and inspections system on the safety of MDs should be strengthened by the national medicines agency, since monitoring safety of MD is paramount.

### New EU regulation on MDs

Recent EU legislation on medical devices has come into force recently: the Regulation 2017/745 of the European Parliament and of the Council of 5<sup>th</sup> April 2017 (not yet transposed).<sup>9</sup> The data and/or analysis in the present study have not emerged from the application of this new regulation, considering this regulation will only be transposed or applied by each of the European countries in the next few years (transition period). Importantly, it seems that the old concepts and definitions are considered in this new regulation; however, Regulation 2017/745 is broader, and among others, it includes more designations regarding medical devices and/or medical purposes. For instance, implants and reagents have been specifically considered MDs, as well as, additional medical purposes have been specifically considered such as monitoring an injury or disability;

investigation, replacement or modification of the anatomy of a pathological process or state; or “providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its main 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”.<sup>8</sup> Thus, as expected, the risk classification was also updated, although MDs are still classified in the same number of classes: I e.g., non-invasive devices not included in the other classes such as non-invasive devices intended to be used as a mechanical barrier, for compression or for absorption of exudates; IIa e.g., non-invasive devices intended for channelling or storing blood, body fluids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body or invasive devices intended for short-term use – and not included in another class; IIb e.g., non-invasive devices intended for modifying the biological or chemical composition of human tissues or cells, blood, other body liquids or other liquids intended for implantation or administration into the body or invasive devices intended for long-term use – and not included in other class; and III e.g., surgically invasive devices intended specifically to control, diagnose, monitor or correct a defect of the heart or the central circulatory system through direct contact with those parts of the body, or total or partial joint replacements. It seems like class I MDs remain, respectively, classified as low-risk devices, IIa and IIb medium-risk devices and class III high-risk devices in accordance with article 51 and Annex VIII of Regulation 2017/745. Another relevant point in this document is the prevision of a specific post-market surveillance system on MDs (Chapter VII), which states that, “for each device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device” (article 83).<sup>9</sup>

Among the possible consequences of the application of Regulation 2017/745 are a higher number of registered MDs and safety alerts on MDs in the EU, since the scope of application of the new Regulation is broader. On the other hand, it is likely that the use of MDs in the EU will tend to become safer because more types of MDs and its respective applications are covered by this new regulation and manufacturers are required to define a post-market surveillance system in accordance with Chapter VII.<sup>9</sup>

#### Additional regulatory recommendations on MDs

The development of databases comprising patient data from MDs use is recommended because it may ensure the generation of automatic alerts, e.g., email and/or phone warnings. Other types of web-based applications may be developed to ensure safe use of MDs in patients. Among others, new applications may be disseminated in the websites of regulatory agencies, which are commonly used to disseminate vigilance information. Social networks may be used to disseminate information on safety or efficacy alerts

of MDs, although more studies on the use of social networks as a way of disseminating safety information on MDs are required. National medicines agencies may recommend that national medicines agencies support/strengthen the publication of more dedicated information about the safety alerts of MDs intended for patients and consumers, since the analyzed safety alerts and EU statistics only provide limited information. For instance, it was not possible to find specific information about the severity of incidents, possible causes, class of device, etc. This information is particularly relevant for healthcare professionals, and the general public in order to increase patient safety.<sup>27</sup>

As far as the regulatory recommendations on MDs here proposed are concerned, the scope of intervention of the national medicines agencies may need to be extended and amplified, for instance with the enforcement of regulation 2017/745.<sup>9</sup> Moreover, private or semi-public organizations may be created in order to supervise the intervention of medicines agencies, NB and/or manufacturers, namely with compulsory enrollment of patients and providers.

#### Study limitations

The MDs from the safety alerts were not checked against the Portuguese Code of the Medical Device (CMD) and its respective Portuguese Nomenclature for Medical Devices (NPDM),<sup>28</sup> because either CMDs or NPDMs were not made available in the safety alerts published by INFARMED, I.P.. However, brands and/or producer names of MDs were presented in the published safety alerts, and almost all of these brands and/or producers were no more available in the CMD Portuguese database (<https://www.infarmed.pt/web/infarmed/pesquisa-dispositivos>)<sup>28</sup> (e.g. PRIMEDIC DefiMonitor XD®, Afvasningsset EPI-SPINAL Pack®, Fenix Facet Resurfacing System® or Thomas Monitor Systems).

Similarly, the existence of a possible combination of devices and the Classes of the MDs of the safety alerts were not specifically investigated, which was due to the limited information on the published alerts. The websites of other competent medicines agencies (European or non-European) were not checked regarding the safety alerts on MDs, although comparative analyses on relevant incidents based on NCARS reports were not carried out.<sup>12</sup> Finally, specific comparisons (e.g., between different MD classes or different severities of events) or safety follow-ups were not specifically carried out.

#### CONCLUSION

The Portuguese Medicines Agency contributes to the citizens' access to quality medical devices, by issuing safety alerts, recommendations and mandatory market withdrawals for unsuitable or unsafe MDs. Despite the limited number of safety alerts in Portugal, cases of counterfeit or falsified MDs have been identified. These situations were followed by corrective actions to ensure public health. The low number of safety alerts in Portugal, compared to other EU countries may be explained by the following potential reasons: (i) some MDs safety problems may have not been

notified by users/patients or healthcare professionals (i.e., underreporting of safety problems with MDs), (ii) limited number of MDs marketed in Portugal probably due to economic restrictions, (iii) the number of inspections to identify falsified or unsafe MDs may be limited or (iv) MDs in the national market may be less prone to safety problems, since not all MDs marketed in the EU are available in Portugal.

Among others, reinforcing vigilance and inspection systems regarding the safety of MDs is recommended and new regulatory safety recommendations may comprise the compulsory delivery of electronic alerts, such as emails to ensure the reception of safety information by all patients. Moreover, the development of apps or other applications to assist patient use, including optimization of MDs in real-time or the existence of a unique ID code in the EU to ensure the traceability of MDs. Further studies are required to confirm these preliminary results.

## DISCLOSURE

A chapter on a similar topic was published in: Pires C, Duarte D. A regulatory and safety perspective on medical devices. In: Mehdi Khosrow-Pour DB, editor. Encyclopedia

of Information Science and Technology - Chapter 125. 5<sup>th</sup> ed. IGI Global; 2021:1815-26. doi: doi:10.4018/978-1-7998-3479-3.ch125.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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