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A decade of improvement of health legislation for medical devices and its impacts on the health regulation cycle

Uma década de aperfeiçoamento da legislação sanitária de dispositivos médicos e os impactos no ciclo da regulação sanitária

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ABSTRACT

Introduction: The sanitary regulation of medical devices was improved with a focus on sanitary risk, through the simplification of regulatory steps and the reduction of the administrative burden. **Objective:** To evaluate the impacts of the improvement of health legislation during the decade 2012-2021 by three indicators representing government, company, and product. **Method:** The indicators developed to evaluate the health regulation cycle are 1) Anvisa's regulatory performance (by median evaluation time of medical devices); 2) companies' performance in complying with health legislation (by proportion of medical devices not authorized for sale); and 3) evidence of medical device health risk (due to adverse events, technical complaints, health alerts and preventive/ cautionary measures). Influence analyses were carried out with variables associated with regulatory process, company size and medical device characteristics as predictors of the indicators. **Results:** The first indicator shows that the Agency's timing has improved across all risk classes of medical devices. In 2012, the indicator was measured in 73 days (interquartile range 56–111), while in 2021 in 9 days (interquartile range 6–15). The second indicator showed improvement only for medical devices in the low/medium risk classes. The third indicator did not show an increase in health risk for medical devices with the regulatory simplifications adopted in the last decade. The influence analysis indicates that the need for a certificate of good manufacturing practices, company size and need for additional information are the most relevant predictor variables. **Conclusions:** the regulatory results from the legislation on medical devices in the last decade were positive.

KEYWORDS: Medical Device; Sanitary Regulation; Anvisa

RESUMO

Introdução: O regramento sanitário de dispositivos médicos foi aperfeiçoado com foco no risco sanitário, por meio da simplificação de etapas regulatórias e da redução da carga administrativa. **Objetivo:** Avaliar os impactos do aperfeiçoamento da legislação sanitária durante a década 2012-2021 por três indicadores que representam governo, empresa e produto. **Método:** Os indicadores desenvolvidos para avaliar o ciclo de regulação sanitária são: 1) desempenho regulatório da Anvisa (por mediana de tempo de avaliação dos dispositivos médicos); 2) desempenho das empresas no cumprimento da legislação sanitária (por porcentagem de dispositivos médicos não autorizados para comercialização); e 3) evidências de risco sanitário do dispositivo médico (por eventos adversos, queixas técnicas, alertas sanitários e medidas preventivas/cautelares). Foram realizadas análises de influência com variáveis associadas ao processo regulatório, porte da empresa e características do dispositivo médico como preditoras dos indicadores. **Resultados:** O primeiro indicador evidencia que os tempos da Agência foram aperfeiçoados em todas as classes de risco de dispositivos médicos. Em 2012, o indicador foi mensurado

em 73 dias (intervalo interquartil 56–111), ao passo que, em 2021, foi de 9 dias (intervalo interquartil 6–15). O segundo indicador apresentou melhora apenas para os dispositivos médicos das classes de risco baixo/médio. O terceiro indicador não demonstrou incremento de risco sanitário para os dispositivos médicos com as simplificações regulatórias adotadas na última década. A análise de influência indica que a necessidade de certificado de boas práticas de fabricação, porte da empresa e a necessidade de informações complementares são as variáveis preditoras mais relevantes. **Conclusões:** Os resultados regulatórios oriundos da legislação sobre dispositivos médicos na última década foram positivos.

PALAVRAS-CHAVE: Dispositivos Médicos; Regulação Sanitária; Anvisa

INTRODUCTION

There are about 2 million types of medical devices on the world market intended for use in human beings for diagnosis, prevention, monitoring, treatment of a disease or for beautification[1]. This diversity is explained, in part, by the composition of the materials, embedded technology, and intended use. Technological innovations arising from nanomaterials, additive manufacturing of 3D printing, wearables, and digital therapies increase the plurality of devices. General purpose products began to play the role of medical devices after the incorporation of medical softwares[2]. Furthermore, the connectivity of medical devices to each other and to the internet has increased the ability to generate a large volume of data of interest.

Health that can support regulatory analyses, such as real-world evidence (RWE). In economic terms, the Brazilian market for medical technologies had revenue estimated at US$7.84 billion for the year 2022. Of this total, US$6.34 billion refer to medical devices[3].

With the mission of protecting and promoting the health of the Brazilian population, currently estimated at more than 213 million inhabitants, the Brazilian National Health Surveillance Agency (Anvisa) has, as one of its challenges, the regulation of the medical devices market. The authorization to market a medical device is an act of competence of the Agency[4]. Aspects of safety and efficacy, as well as manufacturing and market, are evaluated. The health legislation required depends on the risk that the medical device poses to the health of the individual or the community. The risk classification adopted by Anvisa is described in Resolution of the Collegiate Board (RDC) No. 185, of October 22, 2001, for medical products and RDC No. 36, of August 26, 2015, for *in vitro* diagnostic products, grading health risk into four classes (I, II, III, and IV), in ascending order of risk. Parameters for risk classification are: elements such as contact time, invasiveness, sterility, application/use site, among others.

The health regulation cycle is guided by the sanitary risk, classified by risk classes. The cycle consists of strategic and continuous interventions, before and after authorization for the commercialization of the medical device. For this, legal instruments are used (for example: regulations, standards, resolutions), granting of rights (authorizations, licenses, registrations), monitoring compliance with these and risk communication[5]. Although these are common actions applied to regulated goods and services, there are particularities in the regulation of medical devices.

The modernization of the legal framework over the current 23 years of Anvisa's existence is a reflection of the sharing of experiences with the main international players (for example: forums) and, recently, the systematization and implementation of the Regulatory Impact Assessment (RIA) and the Regulatory Outcomes Analysis (ARR). The Law of Agencies (Law No. 13,848, of June 26, 2019) and Decree No. 10,411, of June 30, 2020, regulate the use of RIA and ARR to support the preparation of regulations and measure their impacts. As for international regulatory harmonization and convergence, Anvisa is a member of the International Medical Device Regulators Forum (IMDRF), composed of regulatory authorities from Australia, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the United States of America. At the regional level, the agency is part of the *Grupo Mercado Común* (GMC), subgroup No. 11, of the Southern Common Market (MERCOSUR).

According to the World Health Organization, regulatory systems play a key role in ensuring the quality, safety, and efficacy of medical products. Effective regulatory systems are essential components of health systems and contribute to desired public health outcomes and innovation[6]. In this sense, the Organization for Economic Cooperation and Development (OECD) recommends in its reports Reviewing the Stock of Regulation and OECD Best Practice Principles for Regulatory Policy the adoption of ex post evaluation as a relevant tool for decision-making during the implementation of a normative regulation. In this context, the ARR that can be carried out for a set of regulatory and thematic instruments as proposed here stands out[7].

This study aimed to present an overview of the health legislation edited by Anvisa on medical devices during the last decade (2012-2021). Performance indicators of Anvisa and companies that submit their medical devices for assessment by the Agency were associated with the legislation, as well as the health risk indicator of the products.

METHOD

The study carried out is of a retrospective qualitative and quantitative type, of a descriptive nature, focusing on medical devices (equipment subject to health surveillance, materials for use in health, and devices for *in vitro* diagnosis). Analyzes were stratified by risk class. The time frame of this study comprises the

period between January 1, 2012 and December 31, 2021. This period of time fully comprises the last decade, in which sanitary control measures, focused on products with a higher health risk, were implemented[8].

Three indicators were developed in this study to assess the health regulation cycle. The first indicator, Anvisa's regulatory performance, is a temporal measure, calculated in consecutive days, as the median of the times that comprise the period between the date of submission of the request, with the health surveillance inspection fee (TFVS) paid, until the date on which the decision on the authorization to market the product is taken. The time lapse of eventual supplementation of information by the requesting company during the evaluation process is discounted.

The second indicator, the performance of companies in complying with health legislation, is calculated as the percentage of medical devices not authorized for sale in relation to the total number of medical devices submitted for evaluation by Anvisa by companies. The third indicator, the health risk of the product, is calculated based on three indicators, namely: 1) technical complaints and adverse events, in which the technical complaint is the suspected alteration or irregularity of the product, while the adverse event is any unwanted effect resulting from the use of the product; alert communications, in which the alerts are risk communications published on the Anvisa portal, predominantly arising from field actions reported by the companies to Anvisa in order to reduce the risk of occurrence of an adverse event related to the use of the medical device already on the market; and 3) preventive and/or cautionary measures, expressed through the publication of resolutions in the Federal Official Gazette, which are legally supported by Law No. 6,437, of August 20, 1977, and executed by the Agency when there are signs of alteration or adulteration of the product, dealing with the collection, interdiction, seizure, and/or suspension of manufacture, distribution, advertising, and use. They may come from complaints to the Ombudsman, notifications from the Health Surveillance Notification System (Notivisa) and referrals from other Administration bodies.

The health legislation used to contextualize the data was associated with performance and health risk indicators.

Data source

The health legislation related to medical devices was surveyed and revised from the thematic library of the Agency[8] and the data were obtained from different Anvisa information systems. For Anvisa's regulatory performance indicators and companies' performance in complying with health legislation, data were extracted from the Products and Services under Health Surveillance System (Datavisa). For the third indicator (health risk of the product), data were extracted from Notivisa for notifications of technical complaints and adverse events, the Technovigilance System (Sistec) for health alerts, and the Anvisa portal for preventive and cautionary measures.

Study sample

The three indicators evaluated use historical data stored in Anvisa's information systems from 2012 to 2021 as a sample.

The first and second indicators, Anvisa's regulatory performance and companies' performance in complying with health legislation, use as a sample the medical devices evaluated by Anvisa in which the decision on the authorization for the commercialization of the product was taken during the time frame of the study.

In the sample of notifications of technical complaints and adverse events, the search criteria in the Notivisa system were: for product reason for notification – medical-hospital article, medical-hospital equipment, and reagent kit for *in vitro* diagnosis, all with Anvisa registration number and risk classification. The classification groups A, B, C and D of products for *in vitro* diagnosis established by Ordinance No. 8, of January 21, 1996, of the Health Surveillance Department, were mapped to risk classes I, II, III, and IV, respectively, in the samples.

The sample of alerts contains alerts with registration number with Anvisa. For alerts with more than one record number, multiplicity was considered: an alert with more than one record number was counted in the resulting sample in a number equal to the number of record numbers contained in the alert.

For the sample of preventive and cautionary measures, were selected preventive and/or cautionary measures edited due to deviations in the quality of the medical device and/or laboratory reports with unsatisfactory results, as well as non-compliance with good manufacturing practices (GMP). For preventive and/or cautionary measures with more than one medical device, we considered multiplicity: a measure with more than one medical device was counted in the resulting sample in a number equal to the quantity of products contained in the measure.

Influence analysis

An influence analysis of the three developed indicators was carried out, using the following variables as predictors: risk class of the product (I–IV), nomenclature of the medical device at Anvisa (Technical Name[9]), requirement of a Good Manufacturing Practices Certificate (CBPF) to obtain authorization to market the product (Yes/No), need for supplementation by the company during the regulatory evaluation (Yes/No), type of product (Orthopedic Implant/Material for Use in Health/Equipment subject to Health Surveillance/Product for *in vitro* Diagnosis), the year of the decision to authorize the sale of the product (2012–2021), as well as the size of the company with the Federal Revenue of Brazil (RFB) (Microenterprise/Small Company/Others).

The process of extracting, transforming, and loading the data was performed with Python. The influence analysis was performed with machine learning in Microsoft Power BI with the algorithms specified by the manufacturer[10].

RESULTS

Over the 2012-2021 decade, 83,587 medical devices were submitted to Anvisa's assessment and 79,205 products were authorized for sale. Of the submitted medical devices, 31,472 (36.75%) are in risk class I, 34,862 (41.71%) are in risk class II, 12,126 (14.51%) are in risk class III, and 5,127 (6.13%) are in risk class IV. Of the approved medical devices, 30,065 (37.94%) are in risk class I, 34,332 (43.32%) are in risk class II, 10,512 (13.27%) are in risk class III, and 4,336 (5.47%) are in risk class IV. We observed that part of the products approved between 2012-2021 were submitted in years prior to 2012. If we restrict it to only products submitted from 2012 onwards, there are 72,141 medical devices approved by Anvisa between 2012-2021.

In all, 3,783 companies submitted medical devices for evaluation by Anvisa between 2012-2021. According to open data from RFB[11], 890 (23.53%) are micro companies, 1,259 (33.28%) are small companies and 1,634 (43.19%) are classified as other sizes by the RFB. Of the 79,205 approved products, 53,336 (67.34%) did not require manufacturers to have CBPF at the time of approval. In the same context of approved medical devices, 52,726 (66.57%) did not need additional information or clarification about the documents being evaluated in the regulatory process. Finally, 2,168 (2.74%) orthopedic implants, 45,792 (57.81%) materials for use in health, 17,458 (22.04%) products for *in vitro* diagnosis, and 13,790 (17.41%) equipment subject to health surveillance.

Anvisa's regulatory performance

In 2012, Anvisa's regulatory performance indicator was measured in 73 days (interquartile range 56–111), with 70 days (interquartile range 54–90) for risk class I, 69 days (interquartile range 55–96) for risk class II, 149 days (interquartile range 74–340) for risk class III, and 194 days (interquartile range 107–359) for risk class IV. In 2021, the indicator was measured over 9 days (interquartile range 6–15), with 7 days (interquartile range 6–9) for risk class I, 8 days (interquartile range 6–10) for risk class II, 38 days (interquartile range 20–113) for risk class III, and 78 days (interquartile range 13–143) for risk class IV. The improvement in regulatory performance occurred amid an increase in products submitted for the Agency's evaluation during the evaluated period. In 2012, 6,657 products were submitted to evaluation (2,773 of risk class I; 2,757 of risk class II; 768 of risk class III; and 359 of risk class IV). In 2021, 8,895 products were submitted to evaluation (3,380 of risk class I; 3,661 of risk class II; 1,200 of risk class III; and 654 of risk class IV).

The influence analysis indicates that the need for CBPF for the product manufacturer adds 75 days to the regulatory performance indicator. Furthermore, the need for additional information or clarification adds 64 days to the indicator, even though the company's time to present the additional documentation is not being counted, but only the need for a new round of evaluation by Anvisa. On the other hand, when the size of the company that submitted the product for evaluation by Anvisa with the RFB is defined as a micro-entrepreneur, the regulatory performance indicator is reduced by 26 days.

Figure 1 describes Anvisa's regulatory performance indicator between 2012 and 2021, year by year, contextualized with the time frames of the infralegal health legislation for medical devices, whose effects on the health regulation cycle are summarized in Table 1.

Performance in compliance with health legislation by companies

In 2012, the performance indicator in compliance with health legislation by companies that submitted their medical devices to Anvisa's assessment was measured at 10.59%, with 9.44% for risk class I, 8.02% for risk class II, 20.95% for risk class III, and 16.24% for risk class IV. In 2021, it was measured at 11.61%, with 5.5% for risk class I, 7.45% for risk class II, 29.17% for risk class III, and 24.66% for risk class IV.

The influence analysis indicates that the need for CBPF for the product manufacturer adds 20.19% to the performance indicator in compliance with health legislation. When the size of the company that submitted the product for evaluation by Anvisa with the RFB is defined as a micro or small company, the indicator is increased by 15.46% and 11.45%, respectively. The analysis does not indicate a change in the company's performance due to the need for additional information or clarification regarding the documents being evaluated in the regulatory process.

Figure 2 illustrates the performance indicator in compliance with health legislation by companies between 2012 and 2021, year by year, contextualized with the timeframes of infralegal health legislation for medical devices, whose effects on the health regulation cycle are summarized in Table 2.

Medical device health risk evidence

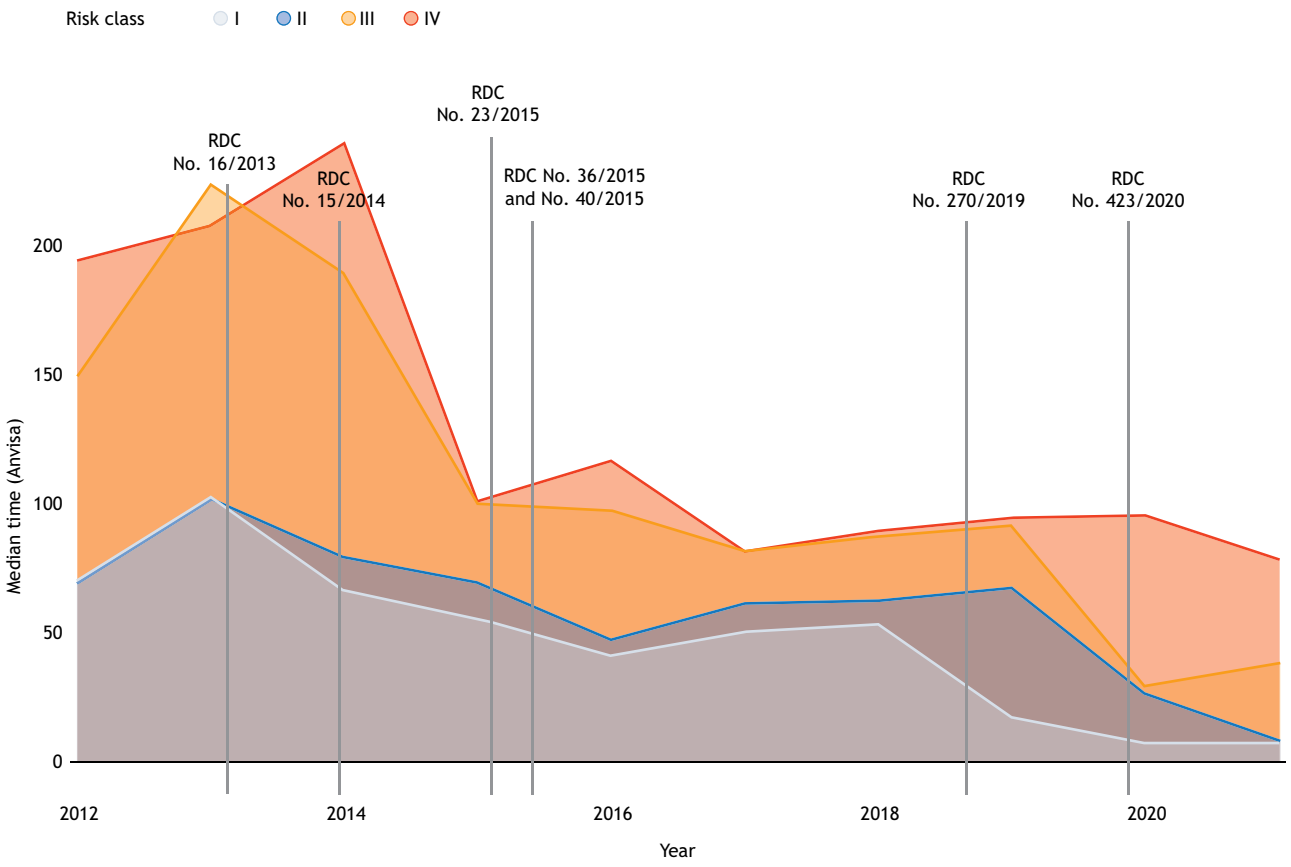
Technical complaints and adverse events

Between 2012 and 2021, Notivisa received 151,233 notifications of technical complaints and adverse events from medical devices, of which 5,371 do not have the risk classification or product registration number with Anvisa and are not considered from now on. Of the remaining 145,862 notifications, 119,648 (82%) refer to technical complaints and 26,214 (18%) refer to adverse events. The results stratified by risk class are shown in Table 2.

The influence analysis indicates that the need for CBPF for the product manufacturer adds six units to the average number of technical complaints. On the other hand, when the size of the company that submitted the product for evaluation by Anvisa is defined as a small company, the average number of technical complaints decreases by seven units. The influence analysis did not indicate the influence analysis did not indicate potential influencers for the mean number of adverse events per product among the predictor variables.

Alert communications

Between 2012 and 2021, the Technovigilance System issued 2,610 medical device alerts, of which 83 do not have the



Source: Elaborated by the authors, 2022.
RDC: Resolution of the Collegiate Board of Directors.

Figure 1. Anvisa regulatory performance indicator, by year and risk class, between 2012 and 2021.

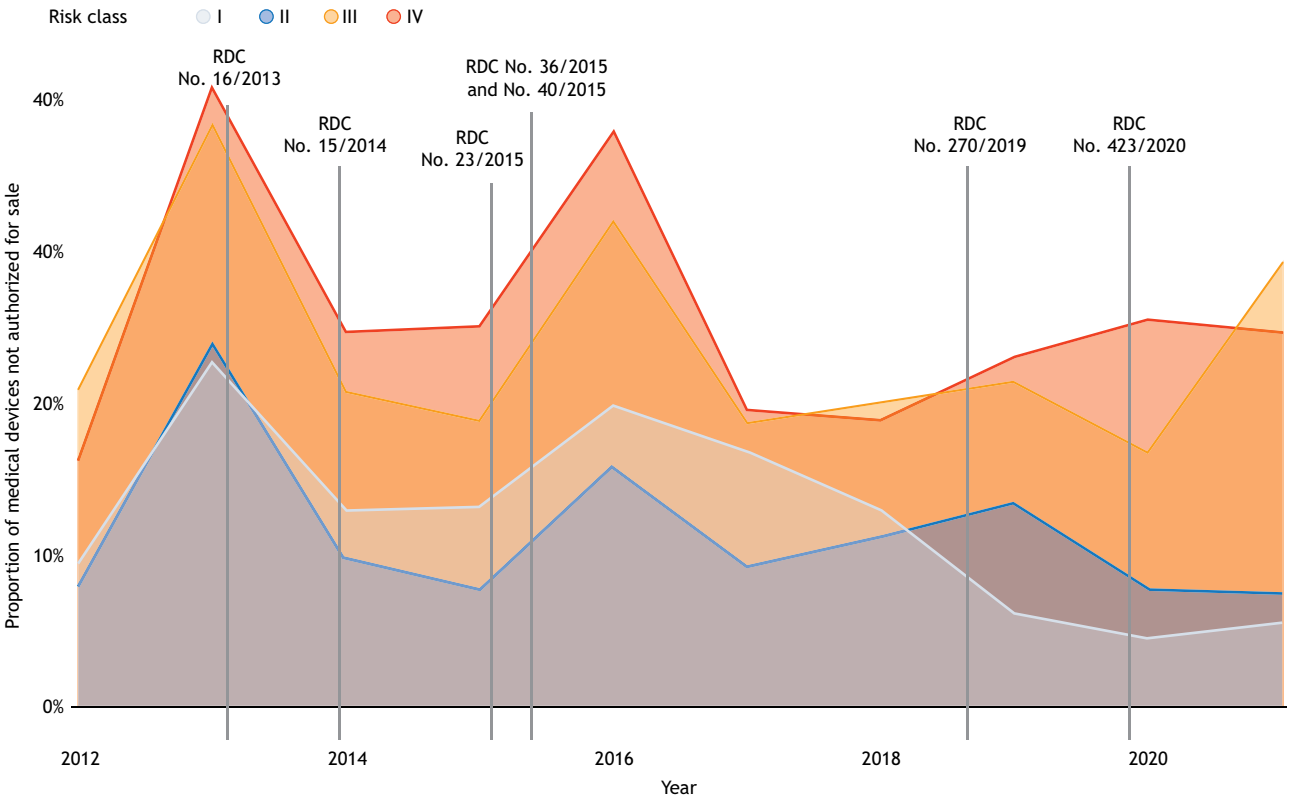
Table 1. Infralegal health legislation for medical devices implemented between 2012 and 2021 with elements of simplification of health regulations and their main effects on the health regulation cycle.

Infralegal health legislation	Effect on the health regulation cycle
RDC No. 23/2012	Made field action notification mandatory
RDC No. 16/2013	Approved the GMP regulation
RDC No. 15/2014	Allowed medical device analysis and GMP process to occur in parallel
RDC No. 23/2015	Adjusted the deadline for completion by the requesting company during the evaluation process to a non-extendable 120 days and discontinued the temporary filing
RDC No. 36/2015 RDC No. 40/2015	Migrated medical devices of risk classes I and II from the registering regime to the registration regime
RDC No. 270/2019	Migrated risk class I medical devices from the registration regime to the notification regime
RDC No. 423/2020	Migrated risk class II medical devices from the registration regime to the notification regime and discontinued the registering regime

Source: Elaborated by the authors, 2022.
GMP: Good Manufacturing Practices Certificate; RDC: Resolution of the Collegiate Board of Directors.

product registration number with Anvisa and are not considered from now on. However, 475 alerts have more than one registration number with Anvisa and each of them are considered as many times as the amount of registration numbers contained in the alert. The results stratified by risk class are shown in Table 2.

The influence analysis indicates that medical devices classified as equipment subject to health surveillance add 1.12 units to the average number of alerts. On the other hand, when the size of the company that submitted the product for evaluation by Anvisa is defined as a micro or small company, the average number of alerts decreases by 0.77 units.



Source: Elaborated by the authors, 2022.
RDC: Resolution of the Collegiate Board of Directors.

Figure 2. Performance indicator for compliance with health legislation by companies by product, by year, between 2012 and 2021.

Table 2. Evidence of the health risk of medical devices by risk class.

Evidence of health risk	Risk class**				
	I	II	III	IV	Total
	N (%)	N (%)	N (%)	N (%)	
Technical complaint					
2012-2021	39,610 (33.11%)	53,436 (44.66%)	17,480 (14.61%)	9,112 (7.62%)	119,648 (100.00%)
2012	3,161 (31.96%)	4,868 (49.22%)	1,182 (11.95%)	680 (6.87%)	9,891 (100.00%)
2021	4,015 (33.85%)	5,054 (42.61%)	1,752 (14.77%)	1,041 (8.78%)	11,862 (100.00%)
Adverse events					
2012-2021	1,243 (4.74%)	4,275 (16.31%)	16,582 (63.26%)	4,114 (15.69%)	26,214 (100.00%)
2012	99 (9.88%)	313 (31.24%)	332 (33.13%)	258 (25.75%)	1,002 (100.00%)
2021	154 (6.05%)	425 (16.70%)	1,177 (46.25%)	789 (31%)	2,545 (100.00%)
Alerts*					
2012-2021	433 (9.22%)	1,666 (35.49%)	1,973 (42.03%)	622 (13.25%)	4,694 (100.00%)
2012	21 (17.07%)	34 (27.64%)	53 (43.09%)	15 (12.20%)	123 (100.00%)
2021	29 (4.26%)	232 (34.07%)	283 (41.56%)	137 (20.12%)	681 (100.00%)
Preventive/cautionary measures					
Unsatisfactory report/ Quality deviation 2012-2021	241 (63.93%)	23 (6.10%)	89 (23.61%)	24 (6.37%)	377 (100.00%)
Noncompliance with GMP 2012-2021	96 (25.46%)	99 (26.26%)	126 (33.42%)	56 (14.85%)	377 (100.00%)

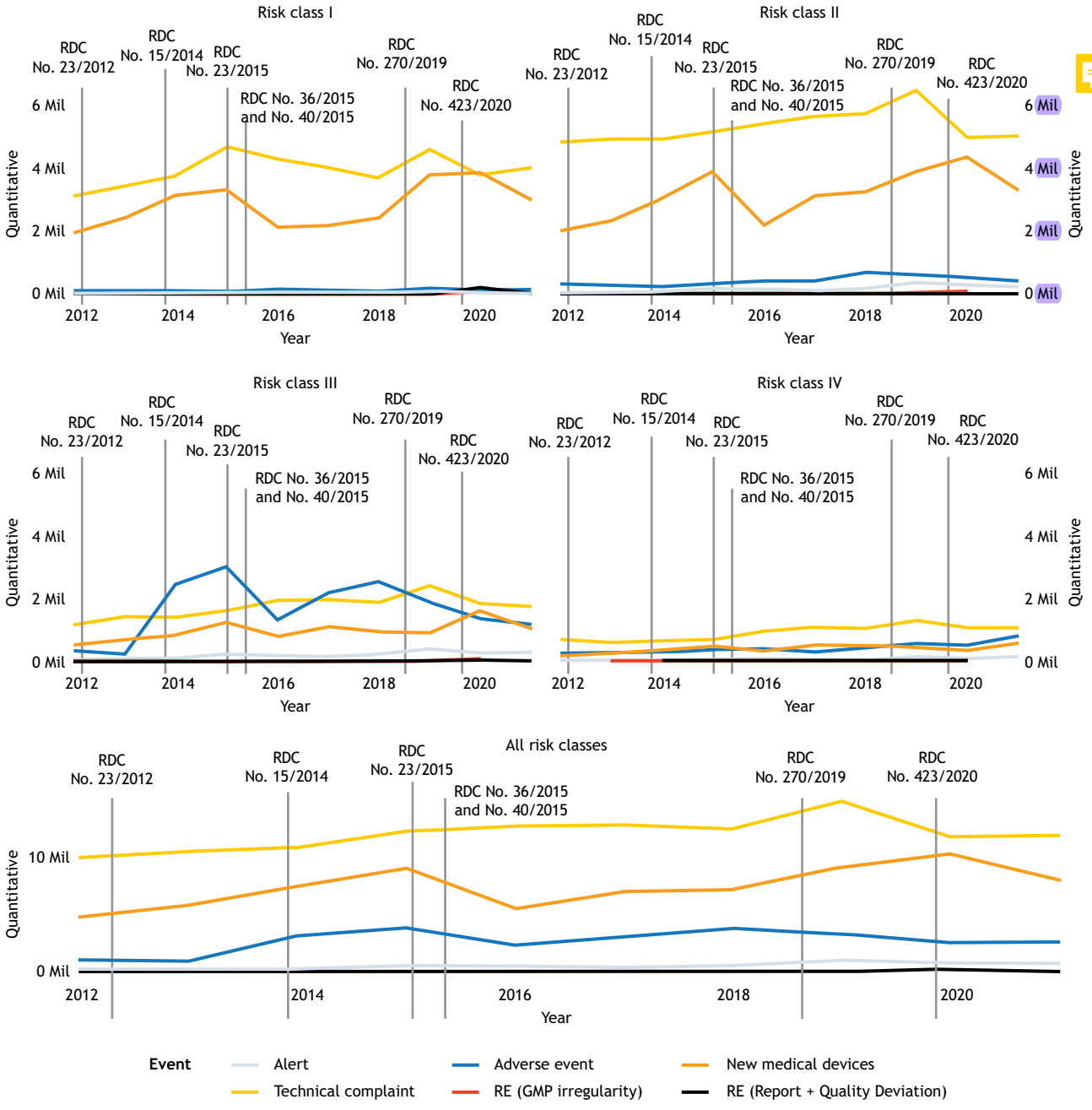
Source: Notivisa (technical complaints and adverse events); Sistec (alerts); Anvisa portal (cautionary and/or preventive measures).
GMP: Good Manufacturing Practices.
*The number of alerts and preventive and/or cautionary measures was broken down by registration number; **Risk classes: class I (low risk), class II (medium risk), class III (high risk), and class IV (maximum risk).

Cautionary or preventive measures

Between 2012 and 2021, Anvisa issued 486 cautionary and/or preventive measures for medical devices, of which 135 deal with unsatisfactory reports and/or quality deviations and 89 deal with non-compliance with GMP. However, 19 of these 224 measures have more than one product listed and each of these measures are considered as many times as the number of products contained in the measure, totaling 377 cautionary and/or preventive measures for medical devices dealing with unsatisfactory reports and/or quality deviations and 377 cautionary or preventive measures for medical devices dealing with non-compliance with GMP. The results stratified by risk class are shown in Table 2.

In 2012, only one cautionary or preventive measure was issued for medical devices dealing with non-compliance with GMP and 14 cautionary or preventive measures for medical devices dealing with unsatisfactory reports and/or quality deviations. In 2021, 32 cautionary and/or preventive measures for medical devices were issued due to unsatisfactory reports and/or quality deviations.

Figure 3 illustrates the evidence of health risk of medical devices authorized for sale between 2012 and 2021, year by year,



Source: Elaborated by the authors, 2022.

Figure 3. Medical device health risk evidence indicator, per year, between 2012 and 2021.

contextualized with the timeframes of infralegal health legislation for medical devices, whose effects on the health regulation cycle are summarized in Table 2.

Study limitations

The time frame of this study comprises the period between January 1, 2012 and December 31, 2021. Between February 4, 2020 and May 22, 2022, the Public Health Emergency of National Importance (ESPIN) was in effect due to human infection with SARS-CoV-2. During this period, Anvisa's infralegal rules were edited as exceptional and temporary health rules, aimed at responding to ESPIN. The effects on the indicators proposed in this study began to be observed but it is necessary to expand the scope to fully observe the effects. We cite as an example the entry of new companies, possibly unfamiliar with the regulatory process, submitting medical devices aimed at combating COVID-19 for evaluation by Anvisa. It is necessary to extend the time frame to assess whether this observed trend materializes for other products. For this reason, this study was limited to not addressing the exceptional and temporary health regulation and its effects on the evaluated indicators.

Other limitations observed in the study refer to variables that contribute to the proposed indicators but of which there is no accurate data available. For the performance indicator on compliance with health legislation by companies, there is no data on the availability of resources from the business units responsible for dealing with regulatory matters. For this reason, we use the substitute variable for company size with the RFB, considering that this can be understood as an indication of the availability of resources. Likewise, Anvisa's availability of resources over the period was not considered, which can serve as a predictor variable for the Agency's regulatory performance indicator, even though it is known that personnel were admitted in 2014 through a public tender and the gradual implementation of the Results-Oriented Management Program with a 20% increase in productivity since 2017. In the context of medical device health risk evidence, accurate data were not found on the number of production units per medical device, imported or domestically produced, which could adjust the numbers of health risk evidence. In this case, we used the surrogate variable medical device nomenclature, considering that it can capture the production volume depending on the characteristics of the set of products of a given nomenclature, for example, being single-use or allowing reuse.

DISCUSSION

Anvisa's regulatory performance

In 2019, the agency responsible for regulating medical devices in Australia (Therapeutic Good Administration - TGA) published a report with the deadlines for regulating medical devices and the time to market among the member countries of the IMDRF12, including Brazil. In this international benchmark, the Australian agency observed that the deadlines of the countries are based on health legislation or are calculated based on historical data, as well as that each country measured its performance differently. That said, time frames should not be compared directly. However, the report establishes an international panorama of regulatory performance indicators, summarized in Table 3.

Anvisa's regulatory performance indicator indicates that the Agency's times have been improved from 2019 to 2021, especially in the evaluation of higher risk products. One of the reasons is attributed to the issue of Decree No. 10,178, of december 18, 2019, which provides for the criteria and procedures for setting the deadline for the tacit approval of a public act of release by lapse of time, including the tacit authorization for the commercialization of a medical device in the national territory. At Anvisa, RDC No. 743, of August 10, 2022, is the normative act that establishes the deadlines for responding to the requirements of public acts of release by the Agency, being 365 days for products for *in vitro* diagnosis, 320 days for materials for

Table 3. Deadlines for medical device regulation among member countries of the International Medical Device Regulators Forum (IMDRF) in 2019.

Risk	Countries							
	Brazil	Australia	United Kingdom	Netherlands	Singapore	Japan	USA	Canada
Low	5 business days	24 h	Undetermined	Undetermined	Undetermined	Undetermined	Undetermined	Upon recieving the certificate
Moderate to high	Approximately 104 business days	20 business days (if selected for audit, 80 business days)	242 business days	193 days	Between 100 and 310 business days	Conformity assessment by the Registered Certification Body	Approximately 280 days	Approximately 11-64 business days
High to maximum	Between 107 and 146 business days	255 business days úteis				Common new devices: 120 days (60 percentiles)	345 business days	

Source: Adapted from the Report on TGA processes and timeframes for the regulation of medical devices and access to market - International benchmarking of Therapeutic Goods Administration in 2019[12,11].

use in health, and 250 days for equipment subject to health surveillance. If the medical device is of risk class I or II, the period decreases to 30 days. The deadline for GMP certification of medical devices is set at 365 days. If the company is a participant in the Medical Device Single Audit Program (MDSAP), the deadline is reduced to 180 days. This definition of deadline establishes a more accurate threshold for improving Anvisa's regulatory performance, since the influence analysis pointed to the need for CBPF of the medical device as the main factor to determine the Agency's regulatory performance indicator. Furthermore, according to the decree, the deadlines may be suspended for completing the procedural instruction only once, when applicable as indicated in RDC No. 743/2022, and the influence analysis pointed to the complementation of the procedural instruction as the second most relevant factor to determine the regulatory performance indicator.

The improvement of infralegal health legislation between 2012 and 2021, discussed below, contributed to the improvement of the Agency's regulatory performance indicator. RDC No. 16, of March 28, 2013, approved the GMP technical regulation for medical devices and RDC No. 15, of March 28, 2014, determined that GMP certificates would no longer be issued for medical devices in risk classes I and II, and allowed the start of the analysis of a medical device dependent on CBPF with the certification request protocol. In this way, it made it possible for the analyzes to take place in parallel, allowing the continuity of an eventual stage of complementation of the procedural instruction while awaiting the certificate. Prior to the issue of RDC No. 23, of June 5, 2015, the deadline for completing the procedural instruction stage was 30 days, extendable for the same period, with the possibility of temporarily filing the petition for up to one year. After editing, the referred period was updated to 120 non-extendable days and the temporary filing mechanism was extinguished. As of 2015, the regulatory processes for authorizing the marketing of lower risk medical devices, specifically those in risk class I and II, began to be simplified. In 2015, Anvisa formalized the registering regime, the one with the fewest regulatory requirements due to the risk, for medical devices in risk classes I and II through RDC No. 36 and No. 40, both of August 26, 2015, respectively for medical products and for *in vitro* diagnostic products. In 2017, Anvisa instituted the notification regime for medical devices of risk class I, exempting them from the analysis that was previously carried out in the registering or cadastre regime, without waiving compliance with health legislation, through RDC No. 270, of February 28, 2019. The notification regime, in brief, comprises the process of communicating the intention to commercialize the medical device through self-declaration of compliance with health legislation. In 2020, the edition of RDC No. 423, of September 16, 2020, extended the notification regime for medical devices of risk class II. Consequently, the registering system was abolished.

Performance in compliance with health legislation by companies

As of 2015, with the migration of medical devices of risk classes I and II from the registering system to the registration system and, subsequently, to the staggered notification system, the performance in compliance with health legislation by companies showed improvement for medical devices of risk classes I and II. Part of this improvement is attributed to the simplification of regulatory rules and another part to the method of evaluating medical devices by sampling, introduced in the notification system[13]. The simplification of regulatory rules and the use of a sampling method for medical devices of risk classes I and II were motivated by the following factors: 1) good historical performance in compliance with health legislation by companies; 2) the need to improve sanitary control of medical devices that pose a greater risk to health; and 3) part of the non-compliance with health legislation in these classes is attributed to administrative aspects, such as unsigned documents and incorrect classification of the medical device to the risk class and/or device nomenclature (technical name).

In the case of medical devices of risk classes III and IV, companies' performance in complying with health legislation is mainly due to: 1) not demonstrating the minimum safety and efficacy requirements, reflected in incomplete results of laboratory tests or insufficient clinical evidence; 2) consularized or apostilled manufacturer's declaration in disagreement with the health regulations or the absence of said declaration; 3) completion of information by companies during the regulatory process carried out after the legally established deadline; 4) non-compliance with RDC No. 156, of August 11, 2006, which deals with the reprocessing of medical devices; and 5) absence of certificate or request for CBPF.

As part of the companies' performance in complying with health legislation is attributable to administrative aspects, the Agency has invested in educational actions, including webinars published on the Anvisa portal[14], specific forms for prior consultation of the sanitary framework, as well as a guide to guide the construction of the documents that are submitted for evaluation by the Agency16.

Another point of interest when it comes to administrative aspects are the costs that the health legislation imposes on companies in sending information to Anvisa, hereinafter referred to as administrative burden, which may interfere with the regulatory performance of the Agency, as well as the performance in complying with health legislation by companies. As an exercise to measure the administrative burden by monetization, Anvisa estimated the administrative burden to comply with RDC No. 185, of October 13, 2006, which deals with the economic monitoring of the implantable medical devices market at R$1,200,000.00/year in the country[17]. At the time, only the understanding of the rules of the health legislation in question contributed with the highest percentage value of the estimated administrative burden: 12.11%. It is asserted that costs are not only of an economic nature, since they can affect performance indicators.

As of 2020, the simplification of health regulations reduced the administrative burden with the publication of: 1) RDC No. 403, of July 21, 2020, eliminating the sworn translation of

documents in English and Spanish; 2) RDC No. 423/2020, dispensing with revalidation for medical devices assessed under the notification regime; 3) RDC No. 438, of November 6, 2020, waiving a certified copy and notarization of documents to be presented to the Agency; and 4) RDC No. 340, of March 6, 2020, enabling immediate implementation in case of alterations to medical devices, considered of medium sanitary relevance, upon notification to Anvisa, as well as exemption from notifying Anvisa in case of alterations to medical devices considered of low sanitary relevance.

Medical device health risk evidence

In the health regulation cycle, the quality of the information provided to Anvisa proves to be extremely important. This serves to base the actions carried out on medical devices authorized for commercialization and to equalize the improvement of health legislation in the evaluation of the safety and effectiveness of the medical device before it is authorized for commercialization. The Sentinel Network is part of this context.

It is a strategic observatory for the collection and management of data on products in use regulated by health surveillance, formed from the collaboration of several actors, and coordinated by Anvisa. Its main tool is Notivisa, which receives notifications of adverse events and technical complaints. Additionally, post-use monitoring data can also support decisions to incorporate technologies based on effectiveness.

Medical devices with consolidated use and functionalities, with a known profile in the market, allow for flexible rules, such as waiving clinical research. In these cases, the monitoring of medical devices authorized to be marketed is paramount for maintaining Anvisa's authorization and for directing the Agency's educational and inspection actions. For example, the monitoring program for COVID-19 diagnostic products, authorized for sale pursuant to RDC No. 379, of April 30, 2020, highlights the importance of monitoring new products on the market. From April 2 to August 18, 2020, 178 batches of rapid tests were analyzed and the analytical study of the sensitivity and specificity trials showed that 57% of the tests presented satisfactory results and 43% presented unsatisfactory results, when compared to the sensitivity and specificity values declared by the manufacturer in the instructions for use13,12. Based on these results, risk mitigation measures were adopted.

While the granting of Anvisa's authorization is an act linked to compliance with health legislation, the incorporation of a technology by the Unified Health System, health plans and health services is a discretionary act generally based on cost-benefit criteria. In this regard, real-world data (RWD) and RWE have been consolidated both for expanding the indications for use approved by regulatory agencies and for incorporation and reimbursement by health systems. Recently, the British agency The National Institute for Health and Care Excellence published a guide for the use of RWE. In Brazil there is still no specific regulation. However, the edition of RDC No. 591, of December 21, 2021, on the Unique Device Identification (UDI) system, strengthened monitoring actions insofar as it enables the tracking of the medical device from production to use and, consequently, can generate data on the actual effect of an indication of use.

Technical complaints and adverse events

Materials for use in health are responsible for 97,204 (81.24%) technical complaints, followed by equipment subject to health surveillance (n = 19,358; 16.18%), product for *in vitro* diagnosis (n = 2.889; 2,41%) and orthopedic implant (n = 197; 0.16%). In the context of adverse events, materials for use in health are responsible for 20,581 (78.51%) adverse events, followed by equipment subject to health surveillance (n = 5,474; 20.88%), orthopedic implants (n = 114; 0.43%) and product for *in vitro* diagnostics (n = 45; 0.17%). These materials form the main type of medical devices with notifications of technical complaints and adverse events because they represent a greater volume of consumables, disposable, or single use in the line of care. There was no increase in the number of notifications of technical complaints and adverse events after the publication of rules for the simplification of regulatory rules issued from 2015 that is proportional to the increase in new medical devices authorized for sale in the national market by the Agency.

Alert communications

Equipment subject to health surveillance is responsible for 2,202 (45.09%) alert communications, followed by material for use in health (n = 1,279; 26.19%), product for *in vitro* diagnosis (n = 1,133; 23.20%) and orthopedic implant (n = 80; 1.64%). In this case, equipment subject to health surveillance forms the main type of medical devices with alert communications depending on the nature of the proposed actions and the device technology that allows for repair when possible. The number of alerts increased by 453.65% from 2012 to 2021.

It is evidence of improvement in the quality management system to monitor and intervene in detected occurrences. RDC No. 23, of April 4, 2012, made mandatory the execution and notification of field actions by medical device registration holders in Brazil. Multinationals are the companies that most request field actions[18], a fact perceived by the influence analysis through the predictor variable of company size with the RFB.

Cautionary or preventive measures

There was no increase in the issue of cautionary or preventive measures after the issue of rules to simplify the regulatory rules issued from 2015 that is proportional to the increase in new medical devices authorized for sale in the national market by Anvisa. However, in 2019, cautionary and/or preventive measures were issued based on the collection health alerts, resulting in the issue of 69 cautionary or preventive measures due to GMP and 32 cautionary or preventive measures due to unsatisfactory reports and/or quality deviations. In 2020, on the occasion of ESPIN in Brazil, 245 cautionary or preventive measures were issued for medical devices that deal with

non-compliance with GMP and 252 cautionary and/or preventive measures for medical devices that deal with unsatisfactory reports and/or quality deviations. Masks for professional use and devices for *in vitro* diagnosis of COVID-19 were the medical devices that were most subject to cautionary or preventive measures in 2020.

CONCLUSIONS

The first years of Anvisa defined the seminal regulations that structure the health regulation of medical devices in Brazil, such as RDC No. 185/2001, for medical products, and RDC No. 206, of November 17, 2006, for products for *in vitro* diagnosis, the latter being eventually replaced by RDC No. 36/2015.

Over the decade defined by the years 2012 to 2021, the health regulation was improved with a focus on health risk, especially with resolutions aimed at simplifying the regulatory regulation and reducing the administrative burden.

The analysis of the indicators was based on the health risk perspective of medical devices. The indicators showed positive results in view of the improvement of health legislation for low and moderate risk medical devices. Anvisa's regulatory performance and companies' performance in complying with health legislation improved without leading to a greater number of notifications of technical complaints and adverse events during the study period.

Consolidating the implementation and expanding the use of *ex post* assessments in its regulatory process is an OECD recommendation for Brazil[19]. In this context, this study contributes to future evaluations of regulatory results of specific standards for medical devices, while outlining the complexity of regulatory rules evaluated by the three developed indicators.

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Author's Contributions

Teixeira LAA, Macedo Filho HB - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.