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Analysis of notifications of technical complaints and preventive health surveillance measures applied during the COVID-19 pandemic in Brazil

Análise das notificações de queixas técnicas e das medidas preventivas de fiscalização sanitária, aplicadas durante a pandemia da COVID-19 no Brasil

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ABSTRACT

Introduction: The consumption of falsified, unregistered, and substandard medicines is a serious public health problem, and it is essential to know the legal enforcement actions related that were taken during the pandemic in Brazil. **Objective:** To Analyze notifications of technical complaints and preventive health measures applied during the Covid-19 pandemic in Brazil. **Method:** Descriptive, quantitative, retrospective study with data from notifications of technical complaints and measures determined by the National Health Regulatory Agency (Anvisa), from 2019 to June 2021. Results: 25,088 notifications of technical complaints about medicines and 562 measures were identified. 314 were classified as class I risk, with high potential to cause serious injury to health, including death. Most unregistered products claim pharmaceutical properties regarding body image, immunity, or information as being "natural" or Traditional Chinese Medicine (TCM). There were 63.3% of actions for advertising and irregular commerce of medicines on the internet. There were 333 measures (59.3%) with an unknown/non-existent company associated, making it impossible to legally hold the offender responsible. The type of enforcement activities the most frequent were: seizure (322), destruction (305) and prohibition (376). The most cited stages of the chain related to post-production, included distribution, commercialization, and use. It was observed that the frequency of risk classification of medicines is significantly different with enforcement actions ($p < 0.001$). **Conclusions:** It is important to: develop strategies aimed at preventing, detecting, and responding to irregular/illegal practices, by reviewing the legal regulatory and the framework; and have greater corporate accountability, traceability mechanisms, effective inspection actions and improvement of the measures adopted by Anvisa to protect the population's health.

KEYWORDS: Post-Market Product Surveillance; Pharmacovigilance; Health Surveillance; Products Retention

RESUMO

Introdução: O consumo de medicamentos falsificados, não registrados e fora do padrão é um grave problema de saúde pública, sendo fundamental conhecer as ações legais de fiscalização sanitária durante a pandemia no Brasil. **Objetivo:** Analisar as notificações de queixas técnicas e as medidas preventivas de fiscalização sanitária, aplicadas durante a pandemia da COVID-19, no Brasil. **Método:** Estudo descritivo, quantitativo, retrospectivo com dados das notificações de queixas técnicas e das medidas determinadas pela Agência Nacional de Vigilância Sanitária (Anvisa), no intervalo de 2019 a junho de 2021. As notificações foram obtidas por meio da Lei de Acesso à Informação, enquanto as medidas preventivas foram coletadas no portal da Anvisa, com a validação dos dados no *site* da imprensa nacional. Resultados: Foram registradas 25.088 notificações de queixas

técnicas de medicamentos e 562 medidas, sendo 314 com elevado potencial de causar sérios danos à saúde, incluindo óbito. A maioria dos produtos não registrados alegam propriedades farmacêuticas relativas à imagem corporal, à imunidade ou ditos "naturais" ou da Medicina Tradicional Chinesa. Dentre as medidas, 63,3% estavam voltadas para propaganda irregular e comércio eletrônico de medicamentos suspeitos. Em cerca de 59,3% das medidas, as empresas não tinham o Cadastro Nacional de Pessoa Jurídica na Receita Federal, o que dificulta a responsabilização legal do infrator. Quanto às ações de fiscalização, as mais frequentes foram: apreensão (322), inutilização (305) e proibição (376). Quanto às medidas de proibição, as mais citadas se relacionam à pós-produção no ciclo produtivo, incluindo distribuição, comercialização e uso. Observa-se que a frequência observada de medicamentos segundo a classificação de risco é significativamente diferente para as várias ações fiscalizatórias ($p < 0,001$). **Conclusões:** Faz-se necessário desenvolver estratégias voltadas à prevenção, detecção e resposta às práticas irregulares/ilícitas, mediante revisão do marco regulatório e do modelo de atuação; maior responsabilização das empresas; mecanismos de rastreabilidade; ações fiscalizatórias efetivas e aprimoramento das medidas adotadas pela Anvisa para proteger a saúde da população.

PALAVRAS-CHAVE: Vigilância de Produtos Comercializados; Farmacovigilância; Vigilância Sanitária; Apreensão de Produtos

INTRODUCTION

In a 2013-2017 study, the World Health Organization (WHO)[1] warned of the impact on the economy and public health of the consumption of substandard, falsified, and unregistered medical products. In this study, more than 1,500 notifications were identified, with antimalarials and antibiotics being the most reported, configuring a global problem that affects all regulatory systems and brings serious health consequences and economic losses to countries[2]. The WHO proposes that actions be taken to prevent, detect and respond effectively to the marketing of substandard, falsified, and unregistered pharmaceutical products[2].

In Brazil, the Brazilian National Health Regulatory Agency (Anvisa) coordinates the regulatory system and, among its attributions, is responsible for the health control of medicines in the country, including authorization/registration, monitoring, and inspection, and can apply measures that interrupt the risk, such as seizure or prohibition of the manufacture, advertising and marketing of products that are potentially harmful to the health of the population[3].

Anvisa registers and investigates notifications of technical complaints (TC) of products, understood as any report of a suspected health irregularity in a product related to its quality, safety or efficacy in post-marketing[4,5]. All falsified products, those not registered by the national regulatory authority (NRA) and those that are outside the specifications or the established standard make up the universe of TC notifications. Although substandard medicines are regularized, they may have a problem with the quality parameters or failures in production processes such as manufacturing, packaging, storage or transport[2,6]. In this sense, Anvisa considers an irregular product to be any that is not up to standard or that does not comply with health legislation and other rules established by the Agency[7].

In the TC screening and investigation process, there is an assessment and classification according to the degree of risk, considering its nature, extent, and severity[4,8]. Class I notifications (high risk of causing serious damage to health, including death) are given absolute priority over the others, with preventive measures aimed at immediate intervention in the transmission of the health risk. Even though the other classes have a lower priority for analysis, it is also important to mention that Risk Class II involves a situation in which there is a high probability that the use of or exposure to a drug may cause temporary harm to health or may be reversible by drug treatment. And Risk Class III is characterized as a situation in which there is a low probability that the use of or exposure to a drug could cause adverse health consequences[8,9].

The adoption of inspection actions is prioritized according to the degree of risk classified at the screening stage and is based on the legal framework of the 1970s, such as Law No. 6.360, of September 23, 1976[10], Law No. 6.437, of August 20, 1977[11], and the resulting resolutions, such as Collegiate Board Resolution (RDC) No. 55, of March 17, 2005[8].

Martins and Galato[12] identified that, in the universe of all notifications received by the Agency, from 2012 to 2017, there was a predominance of drug notifications (38.5%), with 46,818 TC, 1,919 investigation files and 851 preventive measures in which at least one inspection action was determined by Anvisa. Hall et al.[13] also studied the sanitary control of falsified, unregistered or substandard drugs in the American context, identifying 3,045 drugs in a universe of 21,120 recalls reported by the Food and Drug Administration (FDA) between June 2012 and December 2014[13].

In addition, once the COVID-19 pandemic[14] had been declared and Anvisa[15] had applied the exceptions to the specific requirements of good manufacturing practices (GMP) and the import of medicines and pharmaceutical supplies, it became even more of a priority to monitor the behavior of medicines on the market, as well as to check for possible changes in the profile of TC and inspection actions in the period.

Thus, this article aimed to analyze TC notifications and preventive health surveillance measures applied during the COVID-19 pandemic in Brazil.

METHOD

This is a descriptive study based on Anvisa data on TC notifications and preventive health surveillance measures from January 1, 2019, to June 30, 2021.

Access to data on TC notifications per year was made through the Access to Information Law (LAI), using the electronic platform Fala.BR[16], the integrated electronic ombudsman system and access to information (https://falabr.cgu.gov.br), and was officially informed by Anvisa in September/October 2021.

TC notifications go through a screening and investigation process and, if the irregularity is proven, a preventive measure is applied and published in the Federal Official Gazette (DOU) (www.gov.br/imprensanacional/pt-br), by means of a Specific Resolution (SR). According to Anvisa's internal regulations[17], the resolution is an instrument that expresses the administrative decision for the purposes of authorization, approval, certification, cancellation, interdiction, and the application of penalties provided for in health legislation. In this study, the resolution was considered to be the publication of Anvisa's[17] decision to immediately take measures to recall, seize, ban or suspend products that are potentially harmful to health from the market.

The preventive measures (PS) data was collected directly from Anvisa's portal, where it has been possible since the end of 2018 to consult, identify and extract information on irregular products on the market[18].

The types of irregularities extracted from the publications were: unregistered medicines, substandard medicines, falsified medicines, companies without operating authorizations (AFE), and irregular advertising of medicines, including controlled medicines with prescription withholding and deregistration.

For a better understanding and analysis of the information contained in the measures, the following concepts from health legislation were adopted regarding the inspection actions determined by Anvisa:

- Seizure and destruction - action aimed at falsified products, companies without authorization to operate and unregistered products - Law No. 6.360/1976[10] and Law No. 9.782, of January 26, 1999[3].
- Prohibition - action determined for falsifiers, companies without authorization to operate and unregistered products - Law No. 9.782/1999[3] and Law No. 6.437/1977[11].
- Suspension of the import, manufacture, distribution, marketing, and use of medicines/inputs - actions taken for products outside the specifications or quality parameters; with unsatisfactory results in the tax analysis; products contrary to the registration - Law No. 6.360/1976[10] and Law No. 9.782/1999[3].
- Product recalls - withdrawal or removal of substandard or unregistered products from the market - Law No. 6.360/1976[10] and RDC No. 55/2005[8]. It should be noted that there is published information on voluntary recalls carried out by companies.
- Suspension/prohibition/adjustment of advertising - action taken on the irregular advertising of products in different media - Law No. 6.360/1976[10] and Law No. 9.782/1999[3].

It is important to note that a preventive measure is not limited to a single inspection action, but may involve more than one technical decision, depending on the case being investigated, the health violations committed, and the potential risks involved. In addition, measures against substandard medicines refer to the part of irregular products that have been suspended or recalled by Anvisa.

A total of 601 preventive measures on medicines issued by Anvisa between January 2019 and June 2021 were identified, excluding 39 resolutions that were revoked or partially revoked, expired or inactive. Only active resolutions were included in the study, totaling 562 measures for analysis, and these were verified and confirmed on the national press portal. There were measures that did not inform which products and used terms such as "all" or "several", in which case only one unit of the product was counted.

The following data was collected: resolution number; type of irregularity; risk classification; identification of the company responsible for the irregularity, which could be a manufacturer, marketplace, distributor, carrier, or trader; medicines and websites; indications or therapeutic claims and legal enforcement actions (measures) determined by Anvisa.

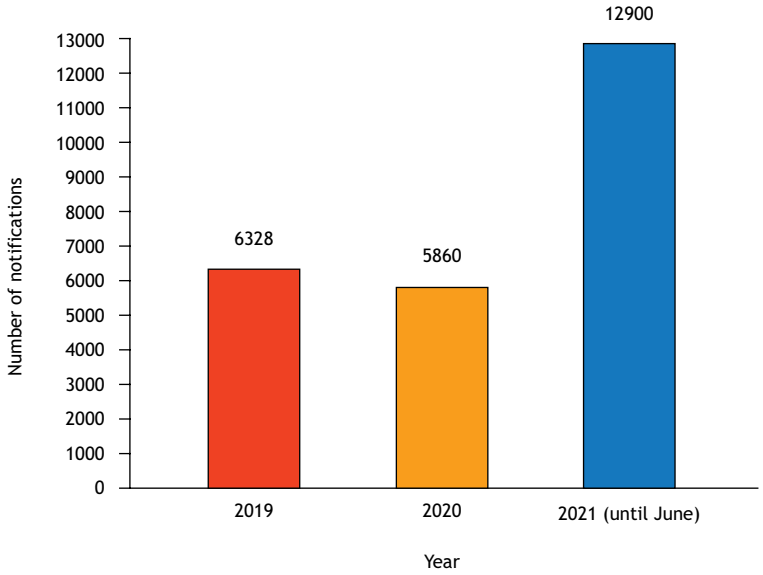
The data was entered into Microsoft Excel® spreadsheets and analyzed using the Jamovi® v.3 descriptive statistics program, in which case the numerical variables were presented as measures of central tendency and dispersion and the categorical variables as absolute numbers and proportions. To determine whether there had been a change in the profile of preventive measures during the period observed, the Chi-square test was used to compare proportions, with p-values < 0.05 being considered significant.

All ethical aspects of research with secondary data were respected, in this case National Health Council Resolution No. 510 of April 7, 2016[19], and the analyses and opinions are the sole responsibility of the authors and do not necessarily represent the official position of the regulatory agency.

RESULTS

In the period analyzed, 25,088 notifications of drug TC were recorded, of which 6,328 in 2019, 5,860 in 2020 and 12,900 by June 2021, including vaccines (Figure 1). It can be seen that in the first half of 2021 there was a 120% increase in notifications when compared to the whole of 2020.

Of the 562 preventive inspection measures analyzed, 169 were published in 2019, 256 in 2020 and 138 by June 2021. These measures involved one or more medicines (maximum of 69 in each measure), totaling approximately 2,035 irregular products



Source: Data provided by Anvisa, through the Access to Information Law (LAI), 2021.

Figure 1. Number of notifications of technical complaints about medicines registered by Anvisa between January 2019 and June 2021 (N = 25,088).

(mean 3.6; SD 7.4: median 1.0), with an average of 678 potentially harmful products released for consumption each year. In 37.9% of the preventive measures, there was no National Registry of Legal Entities (CNPJ) number from the Federal Revenue of Brazil.

Table 1 shows the types of irregularities according to health risk classification, of which 339 (60.3%) were allegedly medicines unregistered with Anvisa, 166 (29.5%) were substandard medicines, and 33 (5.9%) were falsified medicines. Regarding risk, 314 measures were related to products classified as Risk I (55.9%), 156 Risk II (27.7%), and 92 Risk III (16.4%). It should be noted that the majority of these measures were classified as Risk I ($p < 0.001$).

As for the indications or therapeutic claims of unregistered medicines, some claim pharmaceutical properties related to body image, such as slimming and anabolic agents; to boosting immunity or provide information that seeks to confuse the consumer as being "natural products" or from Traditional Chinese Medicine (TCM).

In the analysis of the 339 measures against unregistered medicines, 336 showed that they were being marketed on social networks, e-commerce platforms or online pharmacies without a valid prescription, among other internet channels.

The frequency of the legal enforcement actions determined in the preventive measures per year is shown in Table 2.

Regarding Table 2, looking at recalls in detail, we highlight substandard medicines or quality deviations. In these cases, most of the recalls were voluntary, accounting for 44 (69.8%), 54 (76%), and 14 (77.8%) of the recalls in 2019, 2020, and 2021 (up to June), respectively. Contamination by impurities, known as "nitrosamines", accounted for a third (44/152) of the recall measures, most of which were classified as Risk II.

The prohibition actions detailed in Figure 2A include bans on marketing, use, distribution, and advertising. Figure 2B shows the suspension of marketing, distribution, and use.

Figure 2B, in turn, shows that, similarly to bans, the most common suspensions are of use, marketing, and distribution and account for 160 (93.0%), 159 (92.4%), and 159 (92.4%) in the study period, respectively.

Table 3 shows the relationship between the inspection actions determined by Anvisa and the health risk classification. It can be seen that there is a significant difference between the frequency of inspection actions and the risks involved. Recall and suspension were significantly higher for lower risk medicines (II and III) and actions related to seizure, destruction, and prohibition significantly more frequent for higher risk products (Risk I).

DISCUSSION

Analyzing TC notifications and preventive measures is part of a global strategy by the WHO itself1 which makes it possible to monitor cases of irregular medicines on the market and to learn about the inspection actions carried out by Anvisa to protect the health of the population. It can be seen that in the universe of irregular medicines, there is a predominance of unregistered medicines that are advertised and marketed on the internet.

The findings of this study show that there has been an increase in TC notifications and preventive measures in Brazil, in line with the global trend, according to a WHO report and data from the International Criminal Police Organization (Interpol)[1,20]. The number of irregular medicines involved in inspection actions

Table 1. Distribution of the types of irregularities and the health risk classification, according to the preventive measures published by Anvisa, between 2019 and June 2021 (n = 562).

Type of irregularity	Risk classification			
	Risk I	Risk II	Risk III	Total
	n(%)	n(%)	n(%)	n
Unregistered medicine	263(83.7)	55(35.3)	21(22.8)	339(60.3)
Substandard medication	12(3.9)	91(58.3)	63(68.5)	166(29.5)
Falsified medicine	32(10.2)	0(0.0)	1(1.1)	33(5.9)
Company without operating authorization (AFE)	4(1.3)	1(0.6)	1(1.1)	6(1.1)
Irregular advertising of medicines, including prescription-only medicines	3(0.9)	8(5.1)	5(5.4)	16(2.8)
Deregistration	0	1(0.6)	1(1.1)	2(0.4)
Total	314(100.0)	156(100.0)	92(100.0)	562(100.0)

Source: Anvisa Portal, 2021[17].

Table 2. Distribution of enforcement actions for medicines determined by Anvisa between 2019 and June 2021.

Period	Recall n(%)	Seizure n(%)	Destruction n(%)	Prohibition n(%)	Suspension n(%)
2019	63(41.4)	56(17.4)	49(16.1)	88(23.4)	76(44.2)
2020	71(46.7)	165(51.2)	163(53.4)	181(48.1)	73(42.4)
2021 (until June)	18(11.8)	101(31.4)	93(30.5)	107(28.5)	23(13.4)
Total(*)	152(100.0)	322(100.0)	305(100.0)	376(100.0)	172(100.0)

Source: Anvisa Portal, 2021[17].
*The sum of the items is greater than the number of observations, since the same preventive measure can have several inspection actions.

increased by an annual average of 255% compared to the figures presented in the previous period (2012-2017), as analyzed by Martins and Galato[12]. Corroborating these findings, Rojas-Cortés[21] pointed out that the detection rate in Brazil is quite high, being one of the countries that most identifies falsified, unregistered, or substandard medicines in Latin America[21]. In addition, a study[22] corroborates this when it found that some magistral preparations had commercial names that induce therapeutic actions, such as: capsules for smokers, lion's immunity, emotional control capsules, beauty capsules, etc.[22].

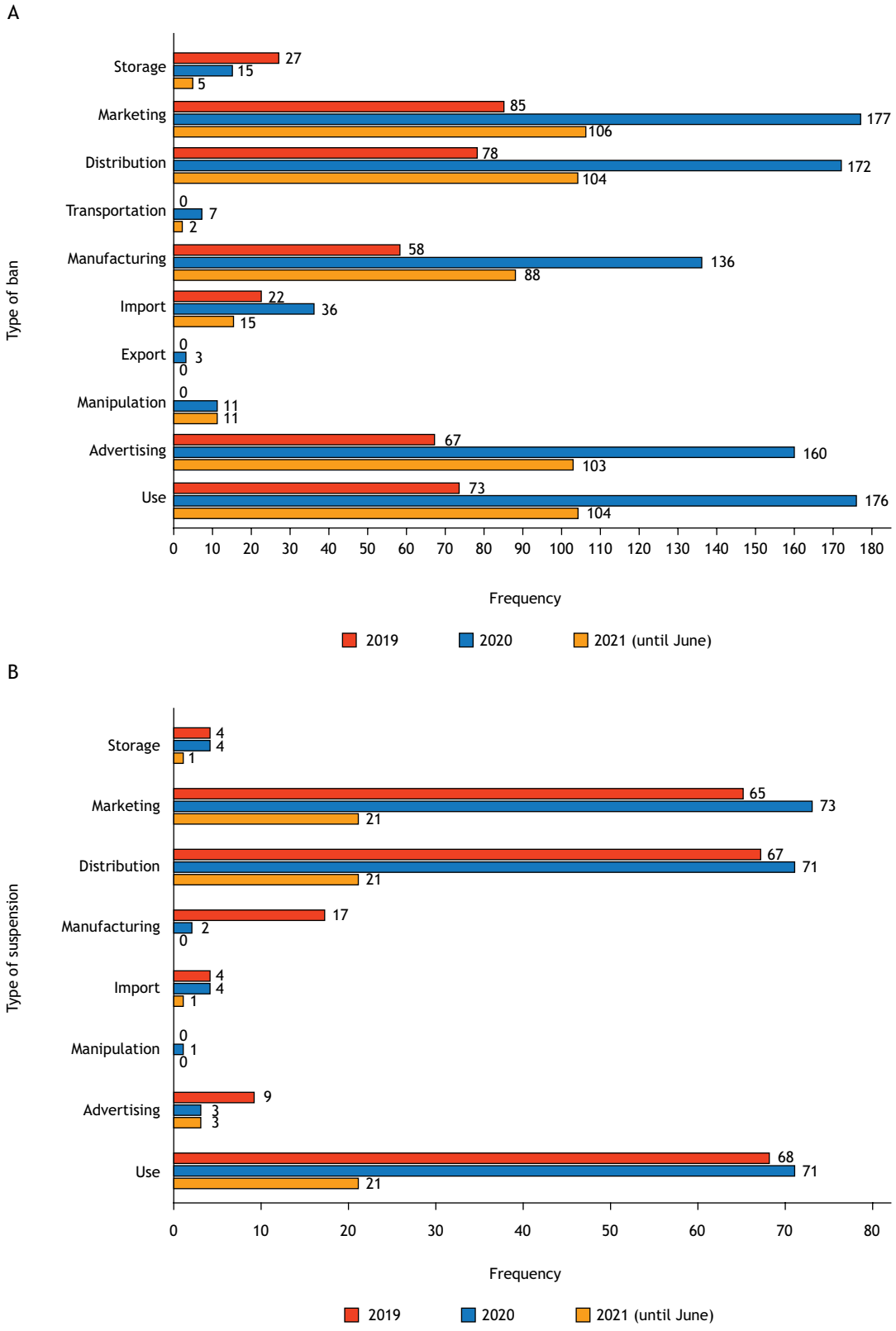
In this interval, Vigimed was implemented in 2019/2020, associated with the wide dissemination of Anvisa's role and enforcement actions among the population by the press and social media, during the COVID-19 pandemic. The implementation of Vigimed and the pandemic may be related to the increase in notifications in the period, corroborated by the study involving the elderly by Souza et al.[23]. According to this study[23], the use of chloroquine and COVID-19 vaccines played an important role in the significant increase in notifications.

In addition, during the pandemic, there has been an increase in access and e-commerce of medical products on a global scale due to social isolation/restriction measures, which has become a concern for all regulatory systems[24].

Reinforcing the important role of health surveillance in social media, Soares et al.[25] described the role of this agency in a municipality in the Northeast and highlighted the actions carried out in management and planning; in health risk control; in regulation itself; in monitoring suspected and confirmed cases of the disease and in situations related to non-compliance with social isolation in the first instance and, as mentioned above, in the process of information, communication, and health education.

In relation to the pandemic, Palácio and Takenami[26] pointed out that there have been numerous barriers to reaching the population through health education. According to the authors, these barriers are related to various situations ranging from technological development to difficulties in adopting hygiene measures or even spreading fake news. These aspects highlight the importance of health surveillance in preventing health problems.

Despite these internal actions, Anvisa suspended international inspections in March 2020 due to the COVID-19 pandemic. The measure was taken to prevent the spread of the virus and protect the health of the employees and companies involved in the inspections. The suspension of international inspections has affected Anvisa's regulatory activities and the approval of new medicines and health products since many processes depend on



Source: Anvisa Portal, 2021[17].

Figure 2. (A) Distribution of drug prohibition actions by stage of the production chain determined by Anvisa between January 2019 and June 2021 (n = 376); (B) Frequency of drug suspension actions by stage of the production chain determined by Anvisa between January 2019 and June 2021 (n = 172).

Table 3. Relationship between drug inspection actions determined by Anvisa and the risk involved, between 2019 and June 2021 (n = 562).

Variable	Risk I n(%)	Risk II n(%)	Risk III n(%)	p-value (*)
Recall				
Yes	16(5,3)	83(53,2)	53(57,6)	< 0,001
No	298(94,6)	73(46,8)	39(42,4)	
Seizure				
Yes	261(83,1)	44(26,7)	17(18,5)	< 0,001
No	53(16,9)	112(73,3)	75(81,5)	
Destruction				
Yes	249(79,3)	41(26,3)	15(16,3)	< 0,001
No	65(20,7)	115(73,7)	77(83,7)	
Prohibition				
Yes	293(93,3)	55(35,3)	28(30,4)	< 0,001
No	21(6,7)	101(64,7)	64(69,5)	
Suspension				
Yes	15(4,8)	95(60,9)	62(67,4)	< 0,001
No	299(95,2)	61(39,1)	30(32,6)	

Source: Anvisa Portal, 2021[17].
* Chi-squared test.

these inspections. Anvisa has therefore stepped up its fiscalization activities as an alternative to maintaining the safety and efficacy of products circulating on the market[27]. Cassano and Areda[28] addressed the issue related to the relaxation of GMP and warned about "the responsibility of both companies and health authorities who, together, must seek to ensure the quality of medicines made available to the population[29]" (p. 50).

In this sense, it is essential to reflect on the number of measures identified without a responsible company or non-existent CNPJ, which makes it difficult to hold the offender legally accountable, whoever they may be in the production chain. The lack of identification of the offender, through the CNPJ, can be due to possible incompleteness of the data in the TC notification but mainly to irregular companies, often represented by online sales sites.

It is also necessary to consider the high level of underreporting of TC, since the model of health inspection at the federal level is predominantly of the passive-reactive type, i.e., the process begins after the TC has been notified or the complaint registered and has limited capacity for investigation, fiscal analysis and effective application of penalties1[,29]. Some studies24[,30] consider that drug regulatory systems, police agencies and the judiciary should be agile and act in an integrated and proactive manner in the face of identified irregularities, seeking to protect the population from the consumption of irregular products in Brazil.

This is where health education for health professionals and the population comes in, so that they can suspect any sign of impurity, contamination, or inadequate sealing, among other problems. If something looks suspicious, they should know how to notify the Agency before any further damage to health can actually occur[31,32].

Despite the absence of some information, as noted above, there has been significant progress in Anvisa's SRs when it comes to providing information on risk classification. In the study by Martins and Galato[12], the authors did not provide risk classification because this information was inconstant at the time of the study. However, for this study, it was possible to verify a higher frequency of preventive measures related to situations classified as high risk (Risk I). Similarly, the majority of international studies[21,33,34,35] on restrictions, bans, and recalls of irregular medicines focus on the high-risk classification, with the greatest potential to cause serious damage to health, including deaths. It should be noted that Anvisa uses the international risk classification, practiced internationally by countries such as the USA, UK, Canada, and Portugal, as a way of establishing priorities for decision-making[21,33,34,35].

Although the improvement in the quality of information on health measures is visible, it is not possible to establish the number of products actually seized, rendered unusable, and recalled from the market, making it difficult to analyze the 2,035 irregular medicines identified in this survey with more information.

It was also difficult to establish a profile in the decision-making process for enforcement action regarding the type of suspension and ban, taking into account the stages of the production chain. Some measures cover all stages, others only some, with the most frequent being those that are closest to the end consumer, such as distribution and use. Rojas-Cortes[21] proved

"the hypothesis that the supply chain is most vulnerable at its final node"[21] (p. 7), which facilitates the penetration of unregistered and falsified drugs. "As a drug moves towards the patient throughout the product life cycle, the number of regulatory controls decreases, while the number of stakeholders and transactions increases"[21] (p. 7).

In this sense, it can be inferred that the measures that present the greatest risk tend to be more severe, such as seizure and destruction, generally related to falsified products or products unregistered with Anvisa. The actions determined have a significantly different proportion in relation to the risk involved. In this sense, as most of these measures have been classified as Risk I and, considering that the composition and origin of the products is unknown, their withdrawal from the market should be immediate.

RDC 55/20058 stipulates that it is the obligation of the holder of the registration of the substandard drug to notify and recall all batches of products in the production chain that fall under Risk I and II but not all of the measures studied include a recall order. It can be seen that there is no standardization of legal enforcement actions, which reinforces the findings of Yamamoto's study[36], highlighting that the absence of detailed information on the efforts made to remove or correct the irregular product serves as an important strategy for transparency and protection of the population's health[28]. In this sense, it is important for Anvisa to determine and apply clear criteria for inspection and legal action, which could be carried out by means of a panel of experts based on the recommendations of the WHO[1] and other international agencies.

Regarding substandard medicines, there has been an increase in voluntary recalls by companies, probably as a result of the strengthening and maturing of the Brazilian regulatory system[20]. Among the reasons for this increase was an international alert about contamination by impurities known as "nitrosamines", potentially carcinogenic chemical compounds[37]. Since then, in a proactive move, Anvisa has established rules and implemented the nitrosamine monitoring program, with the aim of deepening investigations with laboratory analysis in the class of angiotensin II receptor antagonists, the "sartans", products used to control high blood pressure, involving the voluntary participation of the production sector to tackle the problem[37]. They accounted for a third (44/152) of the recall measures, most of which were classified as Risk II. At the end of 2019, Anvisa published a preventive measure due to the presence of this impurity in the active pharmaceutical ingredient (API) (Specific Resolution SR No. 3,210/2019), triggering a series of voluntary recalls by regular companies[37]. Similarly, Pinto et al.[38] observed that Anvisa's more frequent inspections led to a greater number of seizures, including those related to deficiencies in good practices, lack of registration or contamination by nitrosamides, as mentioned above.

A limiting factor to greater adherence to voluntary recalls on the part of companies is Anvisa's obligation to assess and initiate sanitary administrative proceedings (PAS), regardless of the type of recall, according to Law No. 6.437/1977[11] and RDC No. 55/2005[8]. In other countries, such as the USA, voluntary recalls account for more than 90% of recalls *of* substandard medicines, and are encouraged, supervised, and evaluated by the regulatory authority[13,31]. However, Nagaich and Sadhna[30] stated that the extensive list of recalls on the FDA/USA website shows that many industries still do not efficiently follow the GMP standards issued by the American agency.

In Brazil, important initiatives have shown promise, such as Vigimed and the implementation of the National Medicines Control System (SNCM), which will enable traceability throughout the medicines chain, making it difficult for falsified medicines to enter the market, for example[28,39].

In this sense, Martins and Teixeira[40] proposed some initiatives to strengthen drug control and inspection actions, such as:

> 1) reviewing the risk management model for medicines in post-marketing/use; 2) strengthening networking between health services for monitoring and communication; 3) systemic analysis of notifications and integration between information systems; and 4) effective implementation of the product traceability system, as it makes it difficult for irregular products to enter the market.

An important limitation is the limited information provided on preventive measures, even though we double-checked each one on both the national press website and Anvisa's website. It was not possible to relate the inspection actions to the therapeutic classes of the main drugs suspected of irregularities. In addition, the data for 2018 was not included due to the incompatibility of the information on the Agency's old portal[18], which will be reformulated in 2019.

CONCLUSIONS

This study provided evidence on a global public health problem, updating information on TC and preventive surveillance measures related to falsified, unregistered or substandard medicines in Brazil.

There was a significant increase in TC notifications over the period studied, and the percentage of voluntary recalls carried out by the company holding the registration also increased.

It can be seen that the number of inspections carried out to recall and suspend potentially harmful medicines has fallen progressively over the years in relation to the total number of health measures, while seizure, destruction and prohibition actions have increased.

To combat the marketing of irregular medicines on the internet, Anvisa implemented a pilot monitoring project at the end of 2021 using an artificial intelligence tool that tracks and notifies such products in the virtual environment (Epinet - Microsoft Power BI).

We recommend greater alignment with the strategies suggested by the WHO worldwide to strengthen the national regulatory system in post-market surveillance of irregular medicines. In addition to expanding the capacity for prevention, detection, and response to substandard, falsified, and unregistered products, with an updated regulatory framework and operating model; greater accountability for companies; use of technologies that increase detection and integration with pharmacovigilance; implementation of traceability mechanisms; actions to communicate the risk to health professionals and the population; effective inspection actions with supervision of the recall of these products from the market and improved quality of information on the preventive measures adopted by Anvisa to protect the health of the population.

REFERENCES

1. World Health Organization – WHO. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: World Health Organization; 2017[acesso 12 jul 2019]. Disponível em: https://www.who.int/publications/i/item/9789241513432
2. World Health Organization – WHO. Organization global surveillance and monitoring system for substandard and falsified medical products. Geneva: World Health Oganization; 2017[acesso 22 ago 2019]. Disponível em: https://www.who.int/medicines/regulation/ssffc/publications/GSMSreport_EN.pdf?ua=1
3. Brasil. Lei No 9.782, de 26 de janeiro de 1999. Define o Sistema Nacional de Vigilância Sanitária, cria a Agência Nacional de Vigilância Sanitária, e dá outras providências. Diário Oficial União. 27 jan 1999.
4. Agência Nacional de Vigilância Sanitária – Anvisa. Diretrizes para investigação de queixas técnicas de medicamentos e aplicação de processo administrativo sanitário. Brasília: Agência Nacional de Vigilância Sanitária; 2010[acesso 20 dez 2021]. Disponível em: https://www.anvisa.gov.br
5. Chieffi AL. Características de uma boa notificação de suspeita de queixa técnica de medicamentos. São Paulo: Centro de Vigilância Sanitaria; 2013.
6. Centro de Vigilância Sanitária – CVS. Apresentação. São Paulo: Centro de Vigilância Sanitária; 2021[acesso 20 dez 2021]. Disponível em: https://www.cvs.saude.sp.gov.br/apresentacao.asp?te_codigo=30
7. Agência Nacional de Vigilância Sanitária – Anvisa. Produtos irregulares: o que são e como identificá-los: cosmetovigilancia. Brasília: Agência Nacional de Vigilância Sanitária; 2019[acesso 8 dez 2021]. Disponível em: http://antigo.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_returnToFullPageURL=http%3A%2F%2Fantigo.anvisa.gov.br%2Fresultado-de-busca%3Fp_auth%3DQii
8. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC N° 55, de 17 de março de 2005. Regulamenta o recolhimento de medicamentos, que possibilite o acompanhamento pelos órgãos do Sistema Nacional de Vigilância Sanitária e pela sociedade Brasília. Diário Oficial União. 18 mar 2005.
9. Agência Nacional de Vigilância Sanitária – Anvisa. Guia prático para identificação de medicamentos irregulares no mercado. Brasília: Agência Nacional de Vigilância Sanitária; 2010.
10. Brasil. Lei Nº 6.360, de 23 de setembro de 1976. Dispõe sobre a vigilância sanitária a que ficam sujeitos os medicamentos, as drogas, os insumos farmacêuticos e correlatos, cosméticos, saneantes e outros produtos, e dá outras providências. Diário Oficial União. 24 set 1976.
11. Brasil. Lei Nº 6.437, de 20 de agosto de 1977. Configura infrações à legislação sanitária federal, estabelece as sanções respectivas, e dá outras providências. Diário Oficial União. 21 ago 1977.
12. Martins MAF, Galato D. Irregularidades dos medicamentos comercializados no Brasil: uma análise das notificações e das medidas sanitárias de 2012 a 2017. Vigil Sanit Debate. 2018;6(4):23-33. https://doi.org/10.22239/2317-269x.01165
13. Hall K, Stewart T, Chang J, Freeman MK. Characteristics of FDA drug recalls: a 30-month analysis. Am J Heal Pharm. 2016;73(4):235-40. https://doi.org/10.2146/ajhp150277
14. World Health Oganization – WHO. Director-general's opening remarks at the media briefing on COVID-19: 11 March 2020. Geneva: World Health Oganization; 2020[acesso 17 mar 2022]. Disponível em: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
15. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 392 de 26 de maio de 2020. Define os critérios e os procedimentos extraordinários e temporários para a aplicação de excepcionalidades a requisitos específicos das boas práticas de fabricação e de importação de medicamentos e insumos farmacêuticos. Diário Oficial União. 28 maio 2020.
16. Controladoria-Geral da União (BR). Fala.BR: plataforma integrada de ouvidoria e acesso a informação: consultar manifestação. Brasília: Controladoria-Geral da União; 2022[acesso 17 mar 2022]. Disponível em: https://falabr.cgu.gov.br/publico/Manifestacao/DetalharManifestacaoPublico

17. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 585, de 10 de dezembro de 2021. Aprova e promulga o regimento interno da Agência Nacional de Vigilância Sanitária – Anvisa e dá outras providências. Diário Oficial União. 15 fev 2021.

18. Agência Nacional de Vigilância Sanitária – Anvisa. Consultas. Brasília: Agência Nacional de Vigilância Sanitária; 2018[acesso 9 dez 2021]. Available from: https://consultas.anvisa.gov.br/#/dossie/

19. Ministério da Saúde (BR). Resolução Nº 510, de 7 de abril de 2016. Dispõe sobre as normas aplicáveis a pesquisas em ciências humanas e sociais cujos procedimentos metodológicos envolvam a utilização de dados diretamente obtidos com os participantes ou de informações identificáveis ou que possam acarretar riscos maiores do que os existentes na vida cotidiana. Dário Oficial União. 8 abr 2016.

20. International Criminal Police Organization – Interpol. Pharmaceutical crime operations. Lyon: International Criminal Police Organization; 2021[acesso 9 dez 2021]. Disponível em: https://www.interpol.int/en/Crimes/Illicit-goods/Pharmaceutical-crime-operations

21. Rojas-Cortés R. Substandard, falsified and unregistered medicines in Latin America, 2017-2018. Rev Panam Salud Publica. 2020;44:1-10. https://doi.org/10.26633/RPSP.2020.125

22. Nagaich U, Sadhna D. Drug recall: an incubus for pharmaceutical companies and the most serious drug recall of history. Int J Pharm Investig. 2015;5(1):1-7. https://doi.org/10.4103/2230-973X.147222

23. Souza BG, Rezende CP, Detoni KB, Capucho HC, Rosa MB, Carmo Júnior NM, Nascimento MMG. Eventos adversos a medicamentos entre idosos no Brasil antes e após o início da pandemia da COVID-19. Vigil Sanit Debate. 2022;10(3):13-21. https://doi.org/10.22239/2317-269x.02045

24. Mackey TK, Aung P, Liang BA. Illicit Internet availability of drugs subject to recall and patient safety consequences. Int J Clin Pharm. 2015;37:1076-85. https://doi.org/10.1007/s11096-015-0154-8

25. Ferreira VES, Mesquita JMC, Parente PD, Costa Filho LG, Lima MGF, Aguiar AM. O agir da vigilância sanitária frente à COVID-19 e o necessário exercício da intersetorialidade. Rev Pol Públicas. 2021;20(Supl.):58-70. https://doi.org/10.36925/sanare.v20i0.1508

26. Palácio MAV, Takenami I. Em tempos de pandemia pela COVID-19: o desafio para a educação em saúde. Vigil Sanit Debate. 2020;8(2):10-5. https://doi.org/10.22239/2317-269X.01530

27. Agência Nacional de Vigilância Sanitária – Anvisa. Relatório inspeção internacional de fabricantes de insumos farmacêuticos ativos (riifa_2020): período da revisão 2020. Brasília: Agência Nacional de Vigilância Sanitária; 2021[acesso 5 abr 2023]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/certificacao-e-fiscalizacao/manuais-e-orientacoes/relatorio-inspecao-internacional-de-fabricantes-de-insumos-farmaceuticos-ativos-riifa-2020#:~:text=Todas%20as%20inspe%C3%A7%C3%B5es%20internacionais%20agendadas,%2D2019%2Dcom%2Dficha

28. Cassano AO, Areda CA. A flexibilização de requisitos brasileiros de boas práticas de fabricação durante a pandemia da COVID-19 sob uma perspectiva comparada. Vigil Sanit Debate. 2020;8(3):44-51. https://doi.org/10.22239/2317-269x.0171

29. Ji Y, Ying H, Farber MS, Yen J, Dews P, Miller RE et al. A Distributed, collaborative intelligent agent system approach for proactive postmarketing drug safety surveillance. IEEE Trans Inf Technol Biomed. 2010;14(3):826-37. https://doi.org/10.1109/TITB.2009.2037007

30. Nayyar GML, Breman JG, Mackey TK, Clark JP, Hajjou M, Littrell M et al. Falsified and substandard drugs: stopping the pandemic. Am J Trop Med Hyg. 2019;100(5):1058-65. https://doi.org/10.4269/ajtmh.18-0981

31. Wang B, Gagne JJ, Choudhry NK. The epidemiology of drug recalls in the United States. Arch Intern Med. 2012;172(14):1110-1. https://doi.org/10.1001/archinternmed.2012.2013

32. Terrie YC. Overview of the fda's drug-recall process. U.S. Pharmacist. 17 set 2019[acesso 30 ago 2020]. Disponível em: https://www.uspharmacist.com/article/overview-of-the-fdas-drugrecall-process

33. Almuzaini T, Sammons H, Choonara I. Quality of medicines in Canada: a retrospective review of risk communication documents (2005-2013). BMJ Open. 2014;4(10):1-9. https://doi.org/10.1136/bmjopen-2014-006088

34. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001-2011). BMJ Open. 2013;3:1-9. https://doi.org/10.1136/bmjopen-2013-002924

35. Eissa ME. Drug recall monitoring and trend analysis: a multidimensional study. Glob J Qual Saf Healthc. 2019;2(2):34-9. https://doi.org/10.4103/JQSH.JQSH_3_19

36. Yamamoto C, Monteiro E, Batista C. Grounded theory: avaliação das causas de recolhimento de medicamentos irregulares pela Agência Nacional de Vigilância Sanitária. Anais 4º Seminário Internacional de Pesquisa e Estudo Qualitativos; 2009, Rio Claro, Brasil. São Paulo: Sociedade de Estudos e Pequisa Qualitativa; 2009.

37. Agência Nacional de Vigilância Sanitária – Anvisa. Anvisa lança programa de monitoramento de nitrosaminas. Brasília: Agência Nacional de Vigilância Sanitária; 2020[acesso 17 mar 2022]. Disponível em: http://antigo.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=6037353&_101_type=content&_101_groupId=2

38. Pinto NN, Resende KA, Couto RO. Insumos farmacêuticos ativos irregulares no Brasil: análise descritiva de 2011 a 2019. Vigil Sanit Debate. 2021;9(1):61-70. https://doi.org/10.22239/2317-269x.0145

39. Melo VAZC, Beteto AL, Gregis C, Rebelo F, Curado V, Rodrigues A et al. Rastreabilidade na cadeia de medicamentos brasileira. Bol Inst Saúde. 2020;21(1):211-23.

40. Martins MAF, Teixeira APCP. Desafios e perspectivas na vigilância sanitária pós-comercialização/uso. Vigil Sanit Debate. 2019;7(4):3-9. https://doi.org/10.22239/2317-269X.01425

Authors' Contribution

Padro JL - Conception, planning (study design), acquisition, data analysis, and writing of the work. Galato D, Martins MAF - Conception, planning (study design), data analysis, and writing of the work. Areda CA - Writing the paper. All the authors approved the final version of the work.

Conflict of Interest

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

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