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Irregularities´s drugs marketed in Brazil: an analysis of notifications and sanitary measures from 2012 to 2017

Irregularidades dos medicamentos comercializados no Brasil: uma análise das notificações e das medidas sanitárias de 2012 a 2017

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ABSTRACT

Introduction: The drugs available for consumption must have efficacy, safety and quality, being essential their monitoring after registration. **Objective:** This study analyzed the main irregularities of the medicines, their characteristics, types of sanitary measures, means of verification and therapeutic classes (*Anatomical Therapeutic Chemical*) that have risks of causing damages to the health of the population. **Method:** Descriptive and quantitative study using data from the National Product Notification System (Notivisa), Specific Resolutions in the Official Gazette of the Federal Executive and, in addition, data presented in the Management and Activity Reports of the Brazilian Health Regulatory Agency, with retrospective analysis of the notifications and precautionary measures of drugs that presented irregularities in the period from 2012 to 2017. **Results:** There was a progressive increase in notifications for all products, from 37,419 in 2012 to 54,545 in 2017, and medicines accounted for 38.5% of total notifications. 807 sanitary measures were analyzed, comprising 1,149 drugs and 254 companies. In this universe, 55.9% were medicines that presented quality deviations, evidenced mainly by laboratory analysis (48.9%) or by on-site verification during sanitary inspection (13.3%) and in only 30.6% of the measures, there was voluntary withdrawal by the company. The most frequent therapeutic classes were antibacterial, analgesic and antiviral drugs with 13.2% of the irregular drugs, and the herbal products led the list of unregistered or companies in irregular situation. **Conclusions:** Data pointed to the need for a redesign of the post-market surveillance model and for the implementation of a traceability system, so that there is greater responsibility for marketed pharmaceutical products, and an inhibition of counterfeit trade.

KEYWORDS: Drugs; Pharmacovigilance; Health Surveillance

RESUMO

Introdução: Os medicamentos dispostos ao consumo devem apresentar eficácia, segurança e qualidade, sendo fundamental seu monitoramento após registro. **Objetivo:** Este estudo analisou as principais irregularidades dos medicamentos, características, tipos de medidas sanitárias, meios de verificação e classes terapêuticas (*Anatomical Therapeutic Chemical*) que têm risco de causar danos à saúde da população. **Método:** Estudo descritivo, quantitativo, com análise das notificações e das medidas sanitárias dos medicamentos no período de 2012 a 2017. Utilizou-se dados de domínio público do Sistema Nacional de Notificação de Produtos (Notivisa), das Resoluções Específicas no Diário Oficial da União e dos Relatórios da Agência Nacional de Vigilância Sanitária (Anvisa). **Resultados:** Houve aumento progressivo nas notificações de todos os produtos, de 37.419 em 2012 para 54.545 em 2017, e os medicamentos representaram 38,5% do total de notificações. Foram analisadas 807 medidas sanitárias, compreendendo 1.149 drogas e 254 empresas. Neste universo, 55,9%

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foram de medicamentos que apresentaram desvio de qualidade, comprovado principalmente por meio da análise laboratorial (48,9%) ou pela verificação *in loco* durante inspeção sanitária (13,3%) e em somente 30,6% das medidas houve o recolhimento voluntário pela empresa. As classes terapêuticas mais frequentes foram os antibacterianos, os analgésicos e os antivirais com 13,2% dos medicamentos irregulares, e os produtos à base de plantas lideraram a lista dos sem registro ou de empresas em situação irregular. **Conclusões:** Os dados apontaram para necessidade de redesenho do modelo de vigilância pós-mercado e a implantação do sistema de rastreabilidade, de modo que haja maior responsabilidade pelos medicamentos comercializados no país.

PALAVRAS-CHAVE: Medicamentos; Farmacovigilância; Vigilância Sanitária

INTRODUCTION

Medicines that are made available for consumption should be constantly monitored, as they may, at any given moment, present some type of irregularity. It is the duty of Drug Surveillance, as a science, to investigate actions for the detection, evaluation, understanding and prevention of adverse effects, including technical complaints (TC) or any problems that may arise from the use of medicinal products[1,2,3].

According to the World Health Organization (WHO), the technical complaint is any sanitary change or irregularity or other unlawful practices related to a product or manufacturer that presents a potential risk of causing harm to health[4,5,6]. This concept includes products with quality deviations (changes in appearance, color, odor, taste, number of tablets in the package, volume or presence of foreign body), suspected of being unregistered, manufactured by companies without operation license, counterfeit or the result of other irregular practice[6,7].

In this way, conducting studies that are based on post-use surveillance/marketing of medicines is fundamental, so that product safety can be enhanced by monitoring, evaluating, investigating and communicating health risks to the population. Considering these main problems and distortions, we can determine some particular strategies of sanitary regulation to minimize the risks inherent in the use of medicines[8,9,10].

In many countries, drug surveillance is a multi-criteria analysis process for drug notifications in clinical practice, including information on quality and safety, which fill in some of the gaps in post-market monitoring by regulatory agencies, assisting in the decision-making process in situation like the recall of medicinal products[6,9,11,12,13].

In the United States, in the period from 2012 to 2014, there were a total of 21,120 recalls of products regulated by the US Food and Drug Administration (FDA). Of which 3,045 were pharmaceutical products, in a total of 348 affected companies. The most common reasons for recall were contamination (50.10%), labeling errors (21.87%), adverse reactions (9.81%), defective products (7.06%) and incorrect concentration of active ingredients (6.21%)[7].

In Brazil, there are few studies that are specifically concerned with sanitary measures for irregular drugs in the market. Ribeiro published a study that analyzed the importance of Drug Surveillance during the process of monitoring the post-marketing performance of drugs[14]. The study by Branco et al.[15] described the profile of reports of adverse events (AEs) and TCs, carried out by the 27 Central Laboratories of Public Health (Lacens) of the country in 2008.

Research conducted by Yamamoto et al.[16] examined the market recall records for irregular medicines between the years 2006 to 2009 and pointed out that deviations in product quality are among the most important reasons for recall, as well as having important consequences for public health. Hurtado et al.[17] investigated counterfeit and smuggled medicines in Brazil and found that in 90% of establishments where there was seizure of irregular products there was no pharmacist on duty. This absence demonstrates the importance of respecting sanitary and legal standards, including the obligation of having a trained pharmacist in these services.

In Brazil, the Brazilian Health Regulatory Agency (Anvisa) is competent to evaluate and monitor the safety profile of medicines in order to protect the health of the population through safe, effective and quality products. Furthermore, Anvisa can intervene and apply sanitary measures such as suspension, prohibition, ban and even the recall of drugs with irregularities that are available in the market. The process is systematic. It involves the Brazilian Health Regulatory System (SNVS) and includes receiving complaints, assessing risks and investigating sanitary irregularities related to regulated products and companies[18].

Thus, this study aimed to analyze the characteristics of irregularities in drugs marketed in Brazil, based on TC notifications and preventive measures determined by Anvisa.

METHOD

A descriptive, quantitative, retrospective, two-step study for data collection: the first step addressed TC notifications of drugs and the second addressed measures of sanitary interest that were determined to protect the population from a health risk.

To prepare the historical series of notifications of medicines and the classification in TC and AE, we made a survey of the publications on the electronic website (http://www.anvisa.gov.br/notivisa) of the National Product Notification System (Notivisa), referring to the period from 2012 to 2017. To validate and supplement this sample, data from Anvisa's Management and Activity Reports

(2012 to 2017) were collected and also published and made available on the respective website.

From the documentary survey we could collect data and outline the profile of the notifications by product type. Additionally, we could select only the TCs of medicines and include the data of the investigation dossiers, also found in the Reports. We clarify that notifications regarding food and pesticides did not make up the universe of the sample, since they are registered in other systems. Thus, notifications of drugs, health products, sanitizers, cosmetics, blood and blood components made up the analysis of this study. This set is referred to as "all products", as shown in Figure 1.

The second part of the sample was composed of irregular drug data in the same period range, obtained from Anvisa's website, through the Consolidated Specific Resolutions (SR), published weekly. From these consolidated data, the following variables were extracted: number and date of SR, the motivation of the measure, the name and business name of the manufacturer (when identifiable) and the name and batch of the irregular products. Then, we could access the contents of each RE on the sanitary measure of medicines, published in the Official Gazette (DOU) and to create a database in Microsoft Excel® 2007 spreadsheets. The variables and categories of analysis are presented below, according to definitions found in the website and in the Anvisa Activity Report[18]:

1 - Type of irregularity: (a) quality deviation; b) product without marketing authorization, notification or registration; (c) counterfeit medicine; d) irregular advertising; e) irregular company; and f) canceled registration.

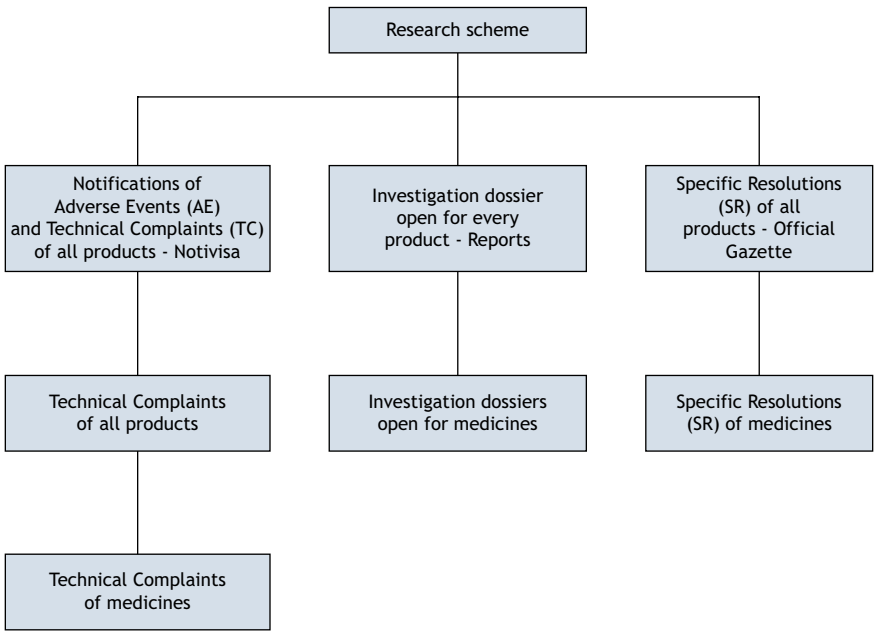
2 - How to check for irregularities: (a) complaint about the manufacturer to the regulatory body; b) fiscal analysis (proven during inspection by the regulatory body and/or laboratory report issued by the Official Laboratory); c) on-site sanitary inspection; d) documentary analysis; e) voluntary notification of the company (notification of the manufacturer to the regulator and voluntary collection of the drug or batch by the holder of the registration); f) notification of the state or cities Health Surveillance Coordination; and g) court ruling.

3 - Preventive measure or health interest measure:

a) *Prohibition/seizure and destruction:* shall be applied to withdraw from the market/recall products considered to be illegal, such as counterfeit products, smuggled products and also clandestine products, manufactured, marketed and distributed by companies without Anvisa's authorization. Legal basis: Article 72, §§ 1 and 2, of Law n. 6.360, of September 23, 1976[19], and article 7, item XV, of Law n. 9.782, of January 26, 1999[20].

b) *Precautionary interdiction*: this is a preventive and temporary measure adopted in case of breach of health legislation or of imminent health risk, which may be partial or total, regarding companies or specific batches of products suspected of irregularity. The length of time necessary to complete the investigation or other measures shall last no more than 90 days. Legal basis: article 7, item XIV, of Law n. 9.782 / 1999[20]; article 23, §§ 2 to 4 and article 25 of Law n. 6.437, of August 20, 1977[21].

c) *Suspension*: applied when the product presents irregularities associated with its manufacturing, importing, distribution, advertising and marketing, or when there is non-compliance with



Source: Prepared by the authors.

Figure 1. Research scheme.

regulatory requirements, like the requirements of good manufacturing practices. Legal basis: article 7 of Law n. 6.360/1976[19].

d) *Recall*: action that aims at the immediate withdrawal of products from the market, after the sanction has been enforced. This is for products that may pose a risk to health or in case of authorization cancellation related to the safety and efficacy of the product. This can be determined by Anvisa and the regulatory bodies in states and municipalities or carried out voluntarily by the company, when the company immediately identifies the deviation. Legal basis: Article 6 of Law n. 6.360/1976[19] and Resolution of the Collegiate Board of Directors (RDC) n. 55, of March 17, 2005 (medicines)[22]. It is important to note that some measures varied widely, ranging from the citation of a specific drug batch to all medicines manufactured and/or marketed by the company.

4 - Classification of the reason(s): (a) counterfeit; b) lack of marketing authorization, notification or registration; c) failure to comply with regulations; d) company without Operation Permit and/or Certificate of Good Practices; and e) announcement of non-approved therapeutic indications.

In the specific case of quality deviations, the reasons were classified as described in the Anvisa website, namely: a) *organoleptic changes* (change in product color, change in odor and taste, turbidity); b) *physico-chemical changes* (disintegration, precipitation, difficult dissolution and homogenization, photosensitivity, thermosensitivity); (c) *overall changes* (foreign particulates, lack of information on the label, authorization problems, damaged packaging material); d) *therapeutic ineffectiveness* (difficult dissolution, low content, drug concentration below label information, inadequate raw material, changes in original formulation); and e) *contamination*[14].

5 - Type of company: (a) manufacturer; b) importer; c) distributor; (d) merchant; and d) unknown.

6 - Therapeutic classification: established according to the Anatomical Therapeutic Chemical (ATC) Classification Index[23], a guide that comprises 14 groups of medicines at the second classification level. This classification is recommended by WHO to be used in drug studies.

It is emphasized that those products qualified for more than one category were classified by the authors according to the reason that stood out in the SR and with greater potential to cause health damage.

The authors chose not to do the risk classification (Class I, II and III) of irregular medicines based on RDC n. 55/2005[22], considering that few SRs presented information about them.

All data from this survey were publicly accessible and collected from August 2017 to January 2018 on the Anvisa website. The data were tabulated using Microsoft® Excel 2007, with dynamic tables, charts, as well as the calculation of percentage distributions, means and standard deviations for descriptive and exploratory data analysis.

Throughout this study, the consistency and veracity of the information were reviewed and validated to ensure the quality of the data collected and the appropriate designations of the analysis categories.

As a study carried out exclusively with secondary data of public domain, it did not have to be approved by the Research Ethics Committee (REC), as recommended by the National Health Council in its Resolution 510 of April 7, 2016. It is fundamental to consider that the results presented in this study are entirely the responsibility of the authors and do not reflect the institutional positioning of Anvisa.

RESULTS AND DISCUSSION

In the period from 2012 to 2017, 274,071 notifications were registered in Notivisa, including TC and AE related to the use of the following products: medicines, cosmetics, sanitizers, blood, blood components and health products. Although there are other channels for receiving complaints about suspicious products, such as ombudsman, e-mail and call center, all were registered in the Notivisa system, according to the reports.

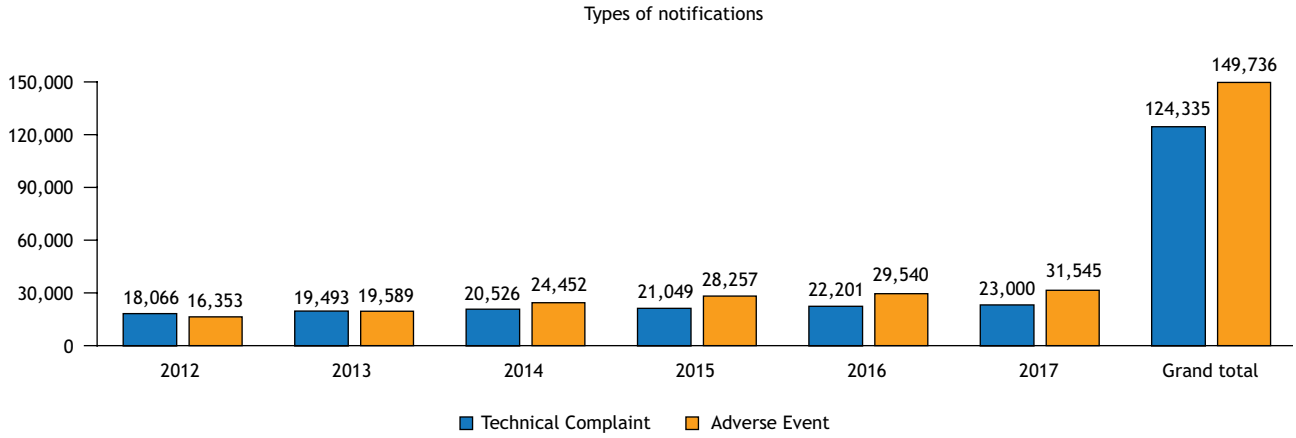
Figure 2 shows the distribution of the notifications in the interval. We found that this distribution increased from 34,419 notifications in 2012 to 54,545 in 2017, which accounts for a 58% (n = 20,126) increase in registrations in the monitoring system. The annual mean of notifications was 45,679, with the standard deviation SD ≈ 7,737.

Although there are many limitations pointed out by other studies on the Notivisa system (intricate system, low acceptability, underreporting, data quality problems, reporting and notification biases with missing product, company or patient information)[5,9,15], the data analysis showed the continuous expansion of the official monitoring system capacity to identify irregularities in regulated products in the market or that caused damages to the health of the population.

In fact, when comparing the annual mean of drug notifications (17,576, SD ≈ 2,743) with that of the United States, we found it to be much lower than that captured by the FDA, which received 1.8 million notifications of a 39-year period, with an annual average of 46,153 notifications, with emphasis also on 151,431 records related to the inefficacy of drugs in the post-market[24].

It was also evident that the AEs, combined with poisoning episodes, accounted for 54.6% (n = 149,736) of the notifications and the TCs, 45.4% (n = 124,335), according to Figure 2.

Analysis of the data presented in Table 1 showed that medicines had the largest share (38.5%, n = 105,455) of all products reported in the period. This can be explained by the obligation of companies holding the registration of medicines, as provided for in art. 4 of RDC n. 55/2005[22], and for the strategy and organization of the Sentinel Network so that other agents, such as health professionals and hospitals, are encouraged to voluntarily notify[25,26].



Source: Notivisa - Anvisa's website. Accessed on: 23 Aug. 2017 and Jan. 31. 2018.

Figure 2. Types of notifications of irregular products from 2012 to 2017.

However, some studies have mentioned underreporting by professionals as a major issue. It occurs due to several factors, like fear, guilt, shame, self-punishment, fear of other people's criticism and litigation, which are common in several countries [5,25,27]. It also corroborates a systematic review done in 2012, which pointed out that the main causes of underreporting are ignorance, insecurity and indifference to events related to the use of medicines[28].

It is important to highlight Notivisa's contribution to the development of Drug Surveillance, since it allows the identification of AEs and TCs related to products subject to health surveillance. It is, therefore, a source of evidence for drug monitoring after its registration and informing the decision making process of the regulatory agency[9,12,27].

The notifications received are evaluated by Anvisa's technical teams regarding the severity, frequency and potential of risk, determining whether they should be investigated or not. This means that some notifications remain under monitoring in the database until a trend analysis sets the time to start the investigation dossier[14,18].

From then on investigation dossiers are created whenever a notification is assessed and rated as a high risk to the health of the population. These are documents that record the diligences, the inquiries to the companies, the records of the investigative inspection and Anvisa's first decision on the TC. In general, the investigative inspection is characterized by on-site inspection (suspicion of quality deviations), collection of samples for fiscal analysis, or special operations (with the Federal Police) regarding suspected falsification, adulteration, product without marketing authorization, among other surveillance actions[18].

Analysis of the research data revealed that the total number of TCs of all products is 24 times higher than the number of research dossiers created between 2012 and 2017 (Table 2). Likewise, there was a small percentage of 4.0% (n = 1,919) of new dossiers in relation to the total of 46,818 TCs about medicines registered in the Notivisa system. Table 2 also showed that among the 1,919 dossiers for drug investigation, only 44.3% (n = 851) had any SR published.

A limitation of this research is that it was not possible to assert that those notified products had their dossiers created and received the respective preventive measures. To do this, we would have to carry out an in-depth study of the sanitary administrative process, with retrospective analysis of each drug that underwent some type of measure during the period, but that was not the objective of the present study.

Irregularities and the imminent risk of causing harm to health require immediate intervention. Sanitary measures are to be adopted, including the suspension or ban of the production, marketing, importing, advertising, and use of medicines, precautionary interdiction of the company and collection of stock on the market[14,21,27]. Whenever suitable, Anvisa gives companies a deadline to fix the non-conformities identified or the recommendations issued. Compliance is usually checked through document analysis, or, in specific cases, by performing a new inspection on the site[18].

In the consolidated report presented on the Anvisa website, 851 SRs of sanitary measures of medicines and irregular pharmaceutical supplies were found in the last six years. Of these, 43 were dismissed from the analysis because they were the abrogation of other SRs previously published. Of this total, three were revoked by court ruling, three by the satisfactory result of the control test, provided for in the fiscal analysis and 37 were revoked by the proof that the company fixed the irregularities detected in the manufacturing process. Of these 37 cases, 27 were through documentary analysis and 10 through sanitary reinspection.

In this sense, the sample consisted of 807 records of sanitary measures (SR), involving 1,149 irregular drugs in the market, and 254 companies, issued between 2012 and 2017. Of these,

Table 1. Notifications according to type of product from 2012 to 2017.

Product Type/Year	2012	2013	2014	2015	2016	2017	Total	%	Annual mean	Standard deviation
Drugs, vaccines and immunoglobulins	13,727	15,273	17,570	17,909	20,019	20,957	105,455	38.5	17,576	2,743
Products for health	11,397	12,457	15,059	17,192	16,353	17,444	89,902	32.8	14,984	2,532
Use of blood or component	8,861	10,955	11,934	13,682	14,665	15,478	75,575	27.6	12,596	2,484
Cosmetics	256	247	226	295	356	369	1,749	0.6	292	50
Sanitizers	178	150	189	228	348	297	1,390	0.5	232	76
Total	34,419	39,082	44,978	49,306	51,741	54,545	274,071	100.0	45,679	7,737

Source: Notivisa – Anvisa's website, access on August 23, 2017, and Jan 31, 2018.

Table 2. Comparison between the total of technical complaints (TC) and technical complaints related to drugs; open investigation dossiers and those that are specific for drugs; Specific Resolutions (SR) and those specific for drugs published from 2012 to 2017.

Year	General			Drugs		
	TC	Dossiers	SR	QT	Dossiers	SR
2012	18,066	777	263	7,278	203	154
2013	19,493	743	291	7,686	233	138
2014	20,526	661	304	8,418	336	141
2015	21,049	567	305	7,425	345	134
2016	22,201	1,135	409	7,788	316	158
2017	23,000	1,362	432	8,223	486	126
Total	124,335	5,245	2,004	46,818	1,919	851

TC: technical complaints; SR: Specific Resolutions
Source: Anvisa's website, access on August 23, 2017, and Jan 31, 2018.

we could not identify 29 companies in their respective resolution. In our total number of products, in 74 SRs we could not quantify a number, since the sanctions were applied to all medicines of the company. In these cases, the minimum of one product per resolution was considered. The ATC classification was not possible for 73 products either, because they were not described in such classification, some of which were informed as plant-based products.

Table 3 shows that among the 807 measures of sanitary interest we analyzed, 65.9% (n = 532) were related to medicines that presented quality deviation, evidenced mainly by fiscal analysis (48.9%, n = 260) or on-site check during sanitary inspection with 13.3% (n = 71). In all, 649 (56.5%) of the 1,149 products were made available for consumption with some type of irregularity (Table 4). This confirms the production and sale of medicines outside of quality standards in Brazil, although they are subject to penalties imposed by health surveillance bodies, as provided for in Law n. 6.437/1977[16].

This was also observed by Fayzrakhmanov in 2015, when 1,109 batches of counterfeit and defective drugs were withdrawn from the market in Russia[29]. According to the author, the detection, investigation and prevention of the use of defective and counterfeit drugs should be systematic rather than periodic. It is necessary to invest in training, cooperation and the continuous exchange of experience between specialists in the field of law and the pharmaceutical sciences in the fight against this phenomenon[29].

Although the fiscal (laboratorial) analysis is an important step of the inspection process, as provided for in Law n. 6.437/1977[22], there was a limited number of fiscal analyses, representing only 32.8% (n = 265) of the measures in a total of 807, according to Table 3.

According to Gemal et al.[30], the unreliability of laboratory support hinders the effective and efficient use of an important stage of the inspection process. Fiscal analysis is the reliable means that scientifically proves the lack of quality deviations and other types of fraud in drug surveillance[30]. Branco et al.[15] emphasize the need for continuous and systematic drug monitoring programs agreed under the SNVS, "in order to carry out laboratory analyses for the evaluation of the quality of products used at national level"[15].

In the light of international experience, different strategies for drug control were revealed. In 2015 alone, the FDA determined 3,772 recalls of defective drugs or batches, versus 74 recall measures in Brazil, for the same reason in that year[31].

The withdrawal of the drugs in the United States occurred voluntarily by the company in most of the aforementioned cases (99.34%)[7], whereas in Brazil the data (Table 3) showed that this voluntary attitude accounted for 30.6% (n = 163) of the 532 sanitary measures due to quality deviation. Based on these findings, we may say that some companies ignore their responsibility and break the law, since in most cases (67.3%, n = 358), the intervention of the health surveillance body was necessary to protect the population from the risks of consuming drugs outside proper quality standards[32].

It is important to clarify that *recall* is not a regulated procedure for drugs in Brazil, despite the existence of RDC n. 55/2005[22]. This standard establishes the minimum requirements for notification of cases to competent authorities and consumers as well as the implementation of the recall for cases of quality deviation

and cancellation of marketing authorization due to problems of efficacy and safety[16,32].

According to some authors, voluntary withdrawal is a great responsibility that requires immediate action and should be adopted by companies more frequently and in a timely manner, reducing the degree of exposure of the population to the risks inherent in defective products[13,32].

The opposite was observed in the identification and notification of most of the measures for counterfeit products (n = 41), in which a percentage of 92.7% (n = 38) was found to have been reported by the manufacturers themselves. After the notification, the investigations for the withdrawal of counterfeit or smuggled drugs are done by Anvisa in partnership with the Federal Police, since it is also a public health crime.

Table 3 also showed the number of measures applied to drugs marketed without marketing authorization, notification or registration in Anvisa (n = 148) and the number of irregular companies in the health surveillance (n = 53).

Considering that some SRs contain determinations applied to more than one drug or respective batches, we could achieve a total of 1,149 products, according to Table 4.

Among the main reasons found in sanitary measures are general changes in the drugs that presented quality deviations, with 28.7% (n = 232). Examples of these are the detection of suspended particles; presence of foreign body in the drug vial/ampule; the packaging is incorrectly labeled; ampules with illegible batch number and/or expiration date etc.[14].

According to Hall et al.[7], contamination is a challenge in drug production and distribution. They also found that in an increasingly interconnected and globalized market, regulation and quality control in drug manufacturing have become even more difficult[7].

The therapeutic ineffectiveness of the drugs was present in 16.5% (n = 190) of the products, with problems like low content of the active ingredient; unsatisfactory result in the dissolution test, drug concentration below that informed on the label and inadequate raw material, among others classified in this category. Authors reported that the procedure adopted in the majority of cases after the occurrence of therapeutic ineffectiveness was the replacement of the drug[5].

The data revealed a worrying number (Table 4) of drugs marketed without marketing authorization, registration or notification in the regulatory body (22.7%, n = 261). That is illegal and poses risks to the health of the population, which is ignorant about the drug's composition and how it is manufactured. Furthermore, there is lack of proof of safety tests, quality and effectiveness of these products.

We noticed that only 62.5% (n = 504) of the published SRs determined withdrawal by Anvisa, in a total of 753 drugs or batches. In this sense, this fact has shown a critical dimension in the inspection process, and it is essential to adopt the appropriate sanitary measures and to determine the full withdrawal of the drugs once there is proven irregularity or suspected fraud[21,32].

Macedo et al.[32] pointed out that the withdrawal of drugs from the market is an important practice of Anvisa's "police power" because "quality deviations jeopardize not only the effectiveness of the products but, depending on the nature of the deviation, of the product and its indications, also the health and life of consumers"[32].

Drugs bans, seizures and destruction totaled 21.4% (n = 173) and were more frequent in products without marketing authorization, notification or registration, and counterfeit, in addition to irregular companies.

Decisions to suspend one or more processes in the production chain (manufacturing, distribution, advertising, marketing) accounted for 68.2% (n = 550) and were more frequent in quality deviations, with 53.2% (n = 429). Precautionary interdictions are temporary (90 days) and occurred in 84 measures. Therapeutic ineffectiveness was the main reason (n = 36).

During the analysis of the SRs, little standardization was found for the issuance of preventive measures, since some presented

Table 3. Sanitary measures according to type and means of verification of drug irregularities from 2012 to 2017 (n = 807).

Type of irregularity	Documentary analysis	Fiscal analysis	Sanitary inspection	Health surveillance notification	Whistleblowing about the manufacturer	Voluntary notification by the company	Total sanitary measures	
							(N)	%
Quality deviation	11	260	71	27	0	163	532	65.9
Product without marketing authorization, notification or registration	140	3	2	3	0	0	148	18.3
Irregular company	32	1	11	9	0	0	53	6.6
Counterfeit drug	2	0	0	1	38	0	41	5.1
Irregular advertising	20	0	0	0	0	0	20	2.5
Registration canceled	10	1	1	0	0	1	13	1.6
Grand total	215	265	85	40	38	164	807	100.0

VISA: Health Surveillance.
Source: Specific Resolutions published in the Official Gazette from 2012 to 2017.

Table 4. Percentage and quantity of medicines and sanitary measures, according to the type of irregularity and the reasons, between 2012 and 2017 (n = 1,149 and 807, respectively).

Type of irregularity and classification of the reason	Irregular drugs (n = 1,149)		Sanitary measures (n = 807)	
	N	%	N	%
Quality deviation	**649**	**56.5**	**532**	**65.9**
General changes	244	21.2	232	28.7
Therapeutic ineffectiveness	190	16.5	157	19.5
Non-compliance with regulations	109	9.5	47	5.8
Organoleptic changes	40	3.5	36	4.5
Contamination	38	3.3	35	4.3
Physical-chemical changes	28	2.4	25	3.1
Irregular company	**148**	**12.9**	**53**	**6.6**
Non-compliance with regulations	101	8.8	20	2.5
Company without Operating Permit and/or Certificate of Good Practices	43	3.7	31	3.8
General changes	4	0.3	2	0.2
Counterfeit drug	**44**	**3.8**	**41**	**5.1**
Counterfeiting	44	3.8	41	5.1
Product without marketing authorization, notification or registration	**261**	**22.7**	**148**	**18.3**
Absence of marketing authorization, notification or registration	233	20.3	126	15.6
Company without Operating Permit and/or Certificate of Good Practices	13	1.1	11	1.4
Announcement of unapproved therapeutic indications	9	0.8	5	0.6
Non-compliance with regulations	6	0.5	6	0.7
Irregular advertising	**31**	**2.7**	**20**	**2.5**
Company without Operating Permit and/or Certificate of Good Practices	4	0.3	2	0.2
Announcement of unapproved therapeutic indications	21	1.8	14	1.7
Non-compliance with regulations	6	0.5	4	0.5
Canceled marketing authorization	**16**	**1.4**	**13**	**1.6**
Non-compliance with regulations	16	1.4	13	1.6
Grand total	**1,149**	**100.0**	**807**	**100.0**

Source: Specific Resolutions published in the Official Gazette from 2012 to 2017.

only the determination of seizure, others involved seizure and destruction, and only slightly over a half ruled that the company withdrew the product from the market. A study by Yamamoto et al.[16] emphasized the need to rethink the standardization of the procedure for the withdrawal of non-compliant drugs, taking into account the variety of criteria for classification of drug recall grounds and including more subjective criteria in the inspection[16].

The survey revealed that manufacturers accounted for 82.9% (n = 669) of sanitary measures in the period 2012 to 2017. There were also 33 importers, 10 distributors, 15 merchants and four websites involved in the advertising/marketing of irregular drugs.

Still in the universe of medicines or batches with quality deviations, antibacterial agents, painkillers and antivirals accounted for 13.2% (n = 152), with therapeutic ineffectiveness (n = 66) as the main reason for issuing the preventive measure (Table 5).

According to a WHO report, irregular drugs can prolong diseases and disorders, time off work and often promote antimicrobial resistance. In the worst cases, several of which are described in this report, people die either from untreated diseases or because the product itself kills them[4].

Plant-based products and drugs that could not be identified top the list of categories of products marketed without marketing authorization, notification or registration, and of irregular companies with 22.1% (n = 254) of total drugs. In this research, plant-based products are those that claim to use plants for medicinal purposes, whether for treatment, cure or prevention of diseases[33]. Examples of this category are those that promise fast weight loss, "bottled mixes", treatments for various types of diseases, including the cure of AIDS.

Table 5. Drugs according to the Anatomical Therapeutic Chemical (ATC) classification level, according to the type of irregularity and the therapeutic class of the irregular drugs, from 2012 to 2017 (n = 1,149).

Type of irregularity	ATC Classification* (second level)	N	%
Quality deviation**		**649**	**56.4**
	J01 Antibacterials for systemic use	85	13.1
	B05 Blood substitutes and perfusion solutions	47	7.2
	N02 Painkillers	44	6.8
	C05 Vasoprotective drugs	30	4.6
	A02 Antacids, drugs for treatment of peptic ulcer and flatulence	24	3.7
	J05 Antivirals for systemic use	23	3.5
Irregular companies		**148**	**12.8**
	D08 Antiseptics and disinfectants	65	43.9
	Plant-based products***	44	29.7
	Unidentifiable products***	19	12.8
	S01 Ophthalmic products	6	4.1
	B05 Blood substitutes and perfusion solutions	6	4.1
Counterfeit drugs		**44**	**3.8**
	H01 Hypophyseal, hypothalamic and similar hormones	13	29.5
	A14 Anabolic steroids for systemic use	9	20.5
	G04 Urological drugs	8	18.2
	A08 Anti-obesity preparations, excluding diet products	5	11.4
	L01 Antineoplastic agents	3	6.8
Product without marketing authorization, notification or registration		**261**	**22.7**
	Plant-based products***	156	59.8
	Unidentifiable products***	35	13.4
	A12 Mineral supplements	21	8.0
	N07 Other drugs for the nervous system	8	3.1
	A11 Vitamins	5	1.9

* ATC (*Anatomical Therapeutic Chemical Code*); ** Presentation of the first 6/5 results;*** Products not classified by ATC or unidentified for ATC.

Corroborating with some authors, there should be some concern with the consumption of medicinal plants/plant-based products. Because of the popular belief that these products do not pose health risks, they are produced in a homemade manner without going through any system of quality or safety check[17,33].

From the data presented in Table 5, the counterfeit drugs that had the highest frequency (n = 30) were hormones, steroids, erectile dysfunction (urological) drugs and stimulants. Some of these compounds are marketed for numerous treatments without any evidence of safety and efficacy. According to studies, irregular and/or counterfeit drugs may not have any effect, render medical treatments useless or, in more serious cases, severely compromise health, even leading to death[4,17].

In view of the findings described in this study, it is important to emphasize that the results should be interpreted with caution in light of the limitations we pointed out, since only public data and data from indirect sources, such as published reports and SRs, were analyzed. Furthermore, this study does not provide enough information to assess the risks and benefits of a particular drug.

CONCLUSIONS

This study demonstrated that the database of notifications of marketed products is an important source of information for the monitoring and sanitary control of drugs. Nevertheless, the technical capacity of investigation is rather limited according to the data presented.

We could also verify that drug collection done voluntarily by the company (recall) was not very significant, which suggests the need for further studies to identify the reasons for this fact.

In addition to this, market, companies, health surveillance bodies and citizens must change their attitude toward drug surveillance initiatives. There is a pressing need to intensify government efforts to effectively implement a drug traceability system, as required by Law n. 13.410, of December 28, 2016[34].

We found little standardization in the issuance of sanitary measures and, considering the amount of drugs outside quality standards, we recommend the conduction of studies that propose changes to the surveillance model of post-market pharmaceutical products.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.

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