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Irregular active pharmaceutical inputs in Brazil: descriptive analysis from 2011 to 2019

Insumos farmacêuticos ativos irregulares no Brasil: análise descritiva de 2011 a 2019

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ABSTRACT

Introduction: The active pharmaceutical ingredients (API) correspond to the pharmacological part of the medication and the demand for these products has generated great profits for the pharmacochemical industries. As such products are an essential part of the drug production chain, API are subject to inspection by the Brazilian National Health Surveillance Agency (Anvisa) in Brazil. **Objective:** To perform a descriptive analysis of the APIs withdrawn from the Brazilian market between 2011 and 2019, through the Anvisa website in the subsection "irregular products". **Method:** Results were obtained from variables called: manufactures, motivations, products and inspection actions. The results were presented as absolute or relative frequencies, and thus the descriptive profile of the irregular inputs was drawn. **Results:** The majority (80.0%) of the companies with withdrawn APIs are of international origin, with India and China being the predominant countries. The frequency of inspections carried out by Anvisa in the companies showcased strong correlation with amount of inputs withdraw from the market (r = 0.89). The main motivations for withdraw API are the deficiency in Good Manufacturing Practices (GMP), absence of registration and contamination by nitrosamines. Of the 95 irregular inputs evaluated, antimicrobials and antihypertensives (antagonists of angiontensin II) had the greatest frequency of withdrawals. **Conclusions:** Anvisa is in line with the quality standards of other international regulatory agencies and has effectively fulfilled its institutional aim of guaranteeing and promoting the health of the Brazilian population with regard to the inspection of API used in the production of medicines.

KEYWORDS: Good Manufacturing Practices; Quality Management; Drug Recalls; Health Surveillance

RESUMO

Introdução: Os insumos farmacêuticos ativos (API) correspondem à parte farmacológica do medicamento e a demanda por esses produtos tem gerado grandes lucros para as indústrias farmoquímicas. Por fazerem parte essencial da cadeia produtiva de medicamentos, os API estão sujeitos à fiscalização pela Agência Nacional de Vigilância Sanitária (Anvisa) no Brasil. **Objetivo:** Realizar análise descritiva dos API recolhidos no Brasil entre 2011 e 2019, por meio do *website* da Anvisa na subseção de "produtos irregulares". **Método:** Foram obtidos resultados de variáveis denominadas: empresas, motivos, produtos e ações fiscalizadoras. Os resultados foram apresentados como frequências absoluta ou relativa e, dessa forma, traçou-se o perfil descritivo dos insumos irregulares. **Resultados:** A maioria (80,0%) das empresas com API recolhidos é de origem internacional, sendo Índia e China os países predominantes. A frequência de inspeções realizadas pela Anvisa nas empresas apresentou forte correlação com a quantidade de insumos apreendidos (r = 0,89). As principais motivações de recolhimento de API são a deficiência nas Boas Práticas de Fabricação (BPF), ausência de registro e contaminação por nitrosaminas. Dos 95 insumos irregulares avaliados, os antimicrobianos e os anti-hipertensivos (antagonistas de angiontensina II) apresentaram as maiores frequências de recolhimentos. **Conclusões:** A Anvisa está alinhada aos padrões de qualidade de outras agências regulatórias internacionais e tem cumprido com eficiência seu objetivo institucional de garantir e promover a saúde da população brasileira no que concerne à fiscalização de API utilizados na produção de medicamentos.

PALAVRAS-CHAVE: Boas Práticas de Fabricação; Gestão da qualidade; Recolhimento de Medicamentos; Vigilância Sanitária

INTRODUCTION

Pharmaceutical forms are the result of the manipulation of the so-called active pharmaceutical ingredients (API) and of pharmaceutical adjuvants, also called inert or non-active ingredients[1,2]. APIs are chemical substances that have pharmacological properties for medicinal purposes[3]. Worldwide consumption of these inputs in 2016 reached US $ 144 billion[4]. In Brazil, the market for API has shown to be quite heated, so that between 2017 and 2018 there was an increase of US $ 1.4 billion in financial transactions in this sector[5].

APIs represent the beginning of the pharmaceutical industry's production chain and, in order for them to be commercialized, it is necessary for manufacturers to meet quality standards[2]. The Brazilian National Health Surveillance Agency (Anvisa) is the body responsible for sanitary control and for regulating the sale of API in Brazil[5]. This inspection must be strict to ensure that the API used meet the established quality, safety, and efficacy standards, for example, detection of toxic impurities, physical-chemical content analysis, characterization of polymorphs, etc.[6]

To achieve the required quality, Anvisa provides producers with the Good Manufacturing Practices (GMP) tool. GMP are a set of rules aimed at guiding the production of pharmaceutical inputs and products with adequate quality standards[7]. These rules must be complied with at all stages of production to ensure efficiency and safety for users, as well as credibility and competitiveness for companies[8]. For that, the API must be registered before being manufactured and, afterwards, be submitted to registration and inspection[9,10].

Inputs that present a quality deviation from Anvisa, such as a deficiency in GMP, must be withdrawn from the market[9]. In addition, if the inappropriate input is sold in medicines, they must still be withdrawn from the market in accordance with Law No. 6,360, promulgated on September 23, 1976. The withdrawal can be voluntary, coming from the manufacturing company, or it can occur if the inspection agency finds an abnormality of the input during the inspection[11].

After withdrawing the product, Anvisa makes available on its website, in the subsection "irregular products", the information regarding the process of confiscation of the irregular input[12]. Although it is a topic of interest in the context of public health promotion in our country, there is no scientific work to date to analyze the reasons that lead to the withdrawal of API in the Brazilian pharmaceutical market.

Motivated by this technical need and aiming to broaden the debate about the relevance of Anvisa's performance and its institutional role in promoting the protection of the population's health, the objective of this study was to synthesize and descriptively evaluate the information from the withdrawal of API in Brazil between 2011 and 2019.

METHOD

This is a descriptive study carried out in four stages: i) search for information; ii) data collection; iii) data organization and analysis; and iv) discussion and dissemination of results. The information about API withdrawn in Brazil was collected from the electronic site[12] made available free of charge by Anvisa, as follows: in the "Action" field, the item "Inspection and Monitoring" was selected, in the then the item "Consultations and Services" and the sub-item "Irregular products".

All inspection actions (i.e., seizure and destruction, withdrawal, interdiction, suspension, prohibition, and alterations) of falsified and irregular pharmaceutical supplies notified between January 1, 2011 and December 31, 2019 were selected and included in the research. Food, sanitizing agents, medicines, cosmetics, and health products on the website were excluded from the research.

Data were collected regarding: number of the specific resolution; publication date; product; batch; company; manufacturing date; validity; inspection action; observation and motivation. Then, all data were organized, coded and double checked in an electronic spreadsheet. The variables company, reason, product, and inspection action were analyzed as described below:

1. Companies: the first stage determined the total number of companies that presented irregular APIs. Subsequently, the frequency that each company was cited over the course of 9 years (2011-2019) was assessed. Subsequently, the number of companies that are of international and national origin was added, in order to identify which countries have companies with withdrawn APIs.

2. Reason: the total number of reasons presented as justification for classifying the inputs as inadequate was determined. Consecutively, each reason was analyzed as to the number of occurrences in which it was mentioned, highlighting the main reasons that could cause the material to be withdrawn.

3. Product: how many types of inputs were counted, were confiscated, and those described as: "all inputs". Then, the occurrence that each category of input was mentioned was evaluated, thus obtaining the most prevalent types of API. Finally, the overview of the quantity and types of inputs cited per year was elaborated.

4. Inspection action: the total number of inspection actions carried out in the analyzed period was computed and, soon after, it became evident which actions were most commonly applied. Among the actions, the revocation was analyzed individually, in order to determine how many were classified as satisfactory and unsatisfactory.

For the summary, analysis, and interpretation of the data obtained, these were described in the form of absolute and relative frequency (%) and presented in tables and pie charts and vertical bars. Also, to determine the interdependence between the annual frequency of inspections and the quantity of products withdrawn, correlation analyzes and linear regression were

conducted using the least squares technique, considering a 95% confidence interval. The result was expressed using Pearson's correlation coefficient (r).

Then, the results were discussed in the light of national resolutions and studies found in the literature. The methodological path of this research was supported by the National Law on Access to Information (Law No. 12,527, of December 18, 2011)[13] and by Resolution No. 510, of April 7, 2016, of the National Health Council[14].

RESULTS AND DISCUSSION

Companies

Table 1 shows the total number of companies accounted for and identified in Anvisa's inspection records between 2011 and 2019. Of these, 24 were mentioned once, corresponding to 33.8% of the total. Therefore, 66.2% (47) of the companies were repeat offenders, that is, they presented more than one notification. This highlights the frequent occurrence of irregularities and, as a consequence, systematic weaknesses in the quality policy of these manufacturers.

Previous studies on irregular APIs are scarce, especially with regard to the variables analyzed in this study. The high identification margin reaffirms the efficiency in gathering information during inspections and Anvisa's transparency with the Brazilian public. As shown in Table 1 and taking into account the period of analysis of the study, only once all the companies producing somatomedin C (IGF-I) were notified together. The literature shows that in 2015, somatomedin C (IGF-I) was withdrawn from the market, thus Anvisa requested that all companies suspend the production of this API. This measure became necessary since this input did not present an evaluation of therapeutic efficacy and, consequently, Anvisa's approval for commercialization[15].

It is known that, with the implementation of RDC No. 30, of May 15, 2008[16], all APIs must be registered to allow the identification of manufacturers and the traceability of the inputs sold in Brazil. Some companies may not have been registered and, therefore, it was not possible to disclose the manufacturer's identification on the Anvisa portal (Table 1).

Table 1. Absolute and relative values of the companies identified and not identified by the National Health Surveillance Agency between 2011 and 2019.

Companies	Absolute frequency	Relative frequency (%)
Not described on the Anvisa portal*	5	6.5
All companies**	1	1.3
Identified	71	92.2
Total	77	100.0

Source: Anvisa electronic portal, 2020.
* The term refers to those described by Anvisa as "unknown" or "does not apply".
** All manufacturers of somatomedin C (IGF-I) had production suspended.

Among the recognized companies, 57 are of foreign origin and 14 are national. The countries that had the highest prevalence of warned companies were: India (31), China (19), and Brazil (14). Figure 1 shows the relative frequencies of the nationalities of these companies. Studies have shown that over the past decade, 90% of the APIs used in Brazil came from imports, with the majority being of Asian origin[4,17]. The predominance of these Asian countries can be attributed to less stringent labor legislation, in addition to measures to encourage exports and, often, less suitability for GMP and for offering products at reduced prices[18,19].

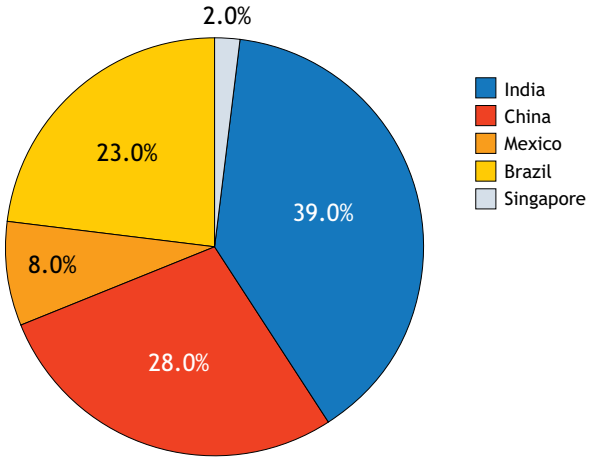
In 2012, the American regulatory agency Food and Drug Administration (FDA) intensified the rigor of inspections at API producers[18,19]. Anvisa, in line with FDA, also implemented greater rigor in the pharmochemical sector[4]. Also in 2012, it inspected 17 Chinese companies, of which eight (47.0%) were disapproved for sanitary disqualification[18].

Figure 2 shows the Brazilian states that presented warned companies, highlighting São Paulo with six companies. This dominance is related to the concentration of the Brazilian pharmochemical pole in the Southeast region, with approximately 81.0% of the industries producing inputs[20]. The city of Anápolis, located in the state of Goiás (Midwest region) is the second largest pharmochemical hub in Brazil[21].

API withdrawal over the years

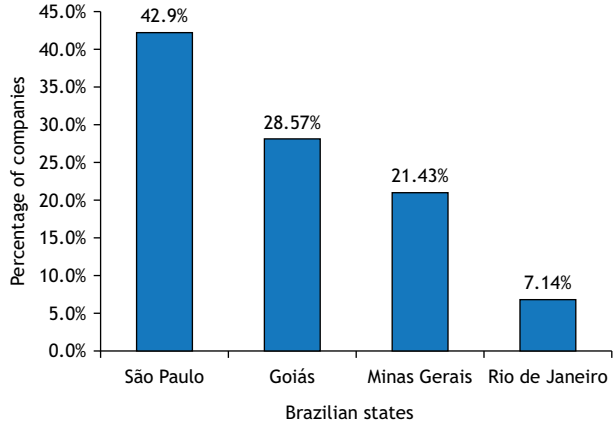
In the analyzed period, 95 inputs were withdrawn. Figure 3 shows a gradual reduction in irregular inputs between the years 2011 to 2014. 2019 was the year with the highest withdrawal rate.

According to Figure 3, the year 2014 presented a drop of 80.0% in the API notification in relation to the previous year. Although exports in the country are not very significant, the pharmochemical sector in 2014 raised US $ 561.4 million, lower than in 2013,



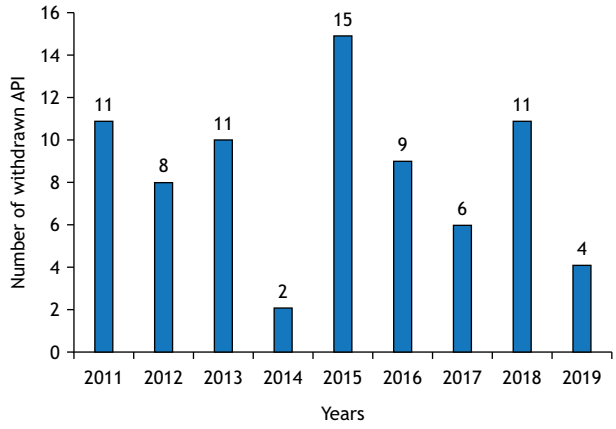
Source: Anvisa electronic portal, 2020.

Figure 1. Relative frequency of companies with active pharmaceutical inputs withdrawn by the Brazilian National Health Surveillance Agency between 2011 and 2019 depending on the manufacturer's nationality.



Source: Anvisa electronic portal, 2020.

Figure 2. Relative frequency of companies with active pharmaceutical inputs withdrawn by the Brazilian National Health Surveillance Agency between 2011 and 2019 depending on the state of the manufacturer.



Source: Anvisa electronic portal, 2020.

Figure 3. Absolute frequency of withdrawal of active pharmaceutical inputs between 2011 and 2019 in Brazil.

when the profit was US $ 642.6 million[5]. This represents a drop of 12.7%, which can be attributed to the lower production of inputs suitable or not for consumption.

In 2015, 12 API were withdrawn more than in the previous year. This increase may be related to the greater number of inspections in pharmochemical industries, which allowed the detection of a greater amount of irregular APIs. In the reports made available by Anvisa, it was observed that, in 2015, 63 companies were inspected, while in 2014 there were 34 companies[22,23].

The increase in 2015 can also be associated with the Normative Instruction (NI) No. 3, of June 3, 2013[24], which has 2014 as the deadline for making the registration petition new inputs. Some companies may not have adapted to the legislation in a timely manner, which resulted in the withdrawal of inputs that were manufactured in disagreement with the legislation in 2015. Another factor that may explain this withdrawal volume is the non-compliance with RDC No. 69, of December 8, 2014[7], which provides for the specific GMP regulation for API.

In the years 2016 and 2017, imports of pharmaceuticals and medicines decreased to US $ 8.4 billion and, in 2018, that value reached US $ 9.8 billion[5]. The increase in imports suggests that greater quantities of inputs were manufactured by our trading partners, which may be associated with production with quality deviations for the reasons already listed and culminated in the increase in API withdrawn in 2018 (Figure 3).

It was estimated a 10% growth in the global pharmaceutical market in 2019, being considered the year of greatest growth in relation to the last five years[25]. In parallel to this favorable economic scenario, there was an increase in the number of inspections by Anvisa in companies in the pharmaceutical industry. In 2018 and 2019, 52 and 61 inspections were observed, respectively[26,27]. In addition, aiming to increase the rigor and effectiveness of its actions, through public consultation (PC) No. 688, of August 12, 2019, Anvisa has discussed new GMP certification criteria for international establishments that manufacture IFA[28]. Taken together, these factors may be the cause of the significant increase in API withdrawal in 2019.

Considering the results obtained for the years 2014, 2015, 2018, and 2019, a strong linear correlation (r = 0.89) was determined between the number of inspections carried out by Anvisa and the number of products withdrawn from the market, that is, the greater the number of companies inspected, the greater the number of irregular products identified.

Irregular inputs profile

The therapeutic API classes withdrawn by Anvisa between 2011 and 2019 in Brazil are shown in Table 2. 81 (85.3%) inputs were identified and 14 (14.7%) were not identified by their respective names. In these cases, Anvisa described the unidentified APIs as “all inputs”. Of the antimicrobial inputs, 17 cephalosporins, three penicillins, four lycosamines, one quinolone, and nine rifampicins were counted. The withdrawn antihypertensive drugs are represented only by the class of angiotensin receptor antagonists, with 11 valsartans, five losartans and one ibersatan. Among anticonvulsants, phenytoin was mentioned four times, once carbamazepine. The H_2 receptor antagonists corresponded only to ranitidine. The antivirals corresponded to two lamivudines and two acyclovir, totaling four inputs.

The high occurrence of antimicrobial withdrawal, in addition to the clinical demand, can also be attributed to NI nº 3/2013[24]. This regulation declares the mandatory registration of ten more inputs, most of which belong to the class of antimicrobials and with a maximum term of petition until 2014. Another factor to be considered is NI No. 35, August 21, 2019[29], related to GMP of sterile drugs, since six cephalosporins were withdrawn for being in disagreement with this regulation.

Antihypertensive drugs were the second most cited class. It is known that the demographic transition causes growth of cardiovascular diseases, therefore, the demand for antihypertensive

Table 2. Main therapeutic classes of active pharmaceutical ingredients withdrawn by the Brazilian National Health Surveillance Agency between 2011 and 2019 in Brazil.

Therapeutic class	Absolute frequency	Relative frequency (%)
Antimicrobials	34	35.8
Antihypertensive drugs	17	17.9
Anticonvulsants	5	5.3
H_2 receptor antagonists	5	5.3
Antivirals	4	4.2
Other classes	30	31.5
Total	95	100.0

Source: Anvisa electronic portal, 2020.

Table 3. Main reasons for the withdrawal of active pharmaceutical ingredients with quality considered unsatisfactory in Brazil between 2011 and 2019 according to the Brazilian National Health Surveillance Agency.

Reasons	Absolute frequency	Relative frequency (%)
Non-compliance with GMP	19	27.9
Failure to comply with Anvisa's regulatory requirements or no registration	10	14.7
Suspension of the certificate of suitability by the European Directorate for the Quality of Medicines & HealthCare	10	14.7
Impurities - nitrosamines	13	19.1
Other reasons	16	23.6
Total	68	100.0

Source: Anvisa electronic portal, 2020.
GMP: Good Manufacturing Practices; Anvisa: Brazilian National Health Surveillance Agency.

API has increased considerably[30]. The sale of medicines for cardiovascular diseases led the market in Brazil in 2016, when the revenues of pharmaceutical companies with the sale of these products reached R $ 5.7 billion[31].

Inspection agencies such as the FDA and the European Directorate for the Quality of Medicines & HealthCare (EDQM) have withdrawn from the antihypertensive market because they find the presence of carcinogenic nitrosamines, mainly in samples of valsartan[32]. In view of the great occurrence of contamination in angiotensin II receptor antagonists, Anvisa decreed RDC No. 283, of May 17, 2019[33] to ensure the control of nitrosamines in inputs marketed in Brazil.

In 2019, contamination by nitrosamines was significant in the ranitidine input. Anvisa, when monitoring the contamination of new inputs, has recommended for information note that all manufacturers review the synthetic route of the API and carry out tests that detect the presence of this type of impurity[34].

Anticonvulsants are used for psychiatric comorbidities, especially epilepsies. It is estimated that epilepsies reach between 0.5 and 1.0% of the population[35]. Although used on a smaller scale than the therapeutic classes mentioned above, these drugs are manufactured regularly, due to continuous use by the consumer. The most common causes that culminated in anticonvulsant withdrawals were the absence of a Good Manufacturing Practices Certificate (CBPF) by manufacturers or irregularities in GMP[19].

Reasons for withdrawal

The main reasons for the withdrawal of API by Anvisa from 2011 to 2019 in Brazil are shown in Table 3. Of the 68 reasons found, 60 (88.2%) were repeated and eight (11.3%) were mentioned only once. Non-compliance with GMP is the main reason for withdrawing API, followed by the identification of potentially toxic impurities. A study looked at 255 Anvisa inspection reports of drug-producing companies between 2015 and 2016. Of these, 12.5% were considered unsatisfactory due to non-compliance with GMP[36]. These precedents corroborate the results presented here.

During the inspection process, poor stability studies, inadequate API quality controls, and unsatisfactory production reports are the main causes for making CBPF admission unfeasible. Normally, when Anvisa finds deficiencies considered to be less critical and amenable to resolution, such as slight deviations in GMP, the company is given 120 days to repair the irregularities. However, if a total of six deficiencies considered serious are found, the CBPF is immediately rejected[36].

Registration allows for greater tracking of input and sanitary control, so it is mandatory to register APIs with Anvisa[9,37]. The implantation of the records started with NI No. 15, of May 26, 2009[38], and, later, with NI No. 3/2013[24], and both define deadlines for registering priority inputs. There are reports that 28.6% of the inspected pharmaceutical industries have some non-compliance with the documentation, including, mainly, the registry[36].

Anvisa adopts high rigor regarding the regulatory practices for pharmaceutical products, among which the API registration, the quality control of the inputs, the stability study, the detection of impurities, and the complete production report are noteworthy[24,36]. In addition, the agency requires the API Forced Degradation Study (FDS), which is essential for granting the registration of the final product, that is, the medication. FDS's objective is to minimize health risk by contributing to guaranteeing the quality, safety, and efficacy of products[39,40,41]. Thus, the literature shows that Anvisa reported, during inspections, a greater number of unsatisfactory results for the drug market than other regulatory authorities, such as the European Medicines Agency (EMA)[36].

Nitrosamines are synthesized from nitrous acid, giving rise to secondary and tertiary amines, due to the variety of amines contained in the raw materials. The presence of this agent is common to occur after long periods of storage, leading to contamination of the input[42]. In the evaluated records, ten cases of identification of N-nitrosodimethylamine (NDMA) and two cases of N-nitrosodiethylamine (NDEA) were reported, which have potential carcinogens when consumed in the long term.

It is estimated that one in every six thousand people who use nitrosamine-contaminated medicine daily and continuously for

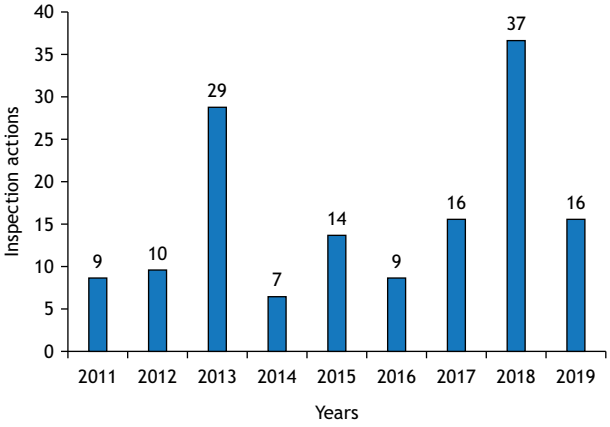
five years may develop cancer, mainly liver[43]. In this context, Anvisa together with the FDA and EMA have instructed to carry out quantification tests, in addition to recommending a reassessment of the synthetic routes of all inputs that belong to the production of the industry[34].

Inspection actions by Anvisa

There was a total of 187 inspection actions distributed in 17 categories. The years with the highest number of shares were 2019 and 2018, followed by 2013, as shown in Figure 4.

The inspection actions that showed greater frequency over nine years were: suspension of imports and suspension of use. One of the ones with the lowest occurrence was the suspension of exports (Table 4).

Inspection actions are sanitary measures that aim to prevent the population from using drugs that pose health risks, guaranteed by Law No. 6,437, of August 20, 1977[44]. Companies with inconsistent regulations are subject to the application of tax actions. In general, preventive actions are classified as suspension, which are adopted until the company settles the pending matters. However, in cases of serious irregularities, such as illegal products, Anvisa can apply corrective actions that include seizure and destruction, prohibiting: distribution, trade, use, or disclosure[45].



Source: Anvisa electronic portal, 2020.

Figure 4. Absolute frequency of inspection actions by the Brazilian National Health Surveillance Agency between 2011 and 2019 in Brazil.

Table 4. Absolute and relative frequencies of the main inspection actions for active pharmaceutical ingredients carried out by the Brazilian National Health Surveillance Agency between 2011 and 2019 in Brazil.

Inspection action	Absolute frequency	Relative frequency (%)
Import suspension	50	26.7
Use suspension	35	18.7
Distribution suspension	33	17.7
Export suspension	1	0.5
Other actions	68	36.4
Total	187	100.0

Source: Anvisa electronic portal, 2020.

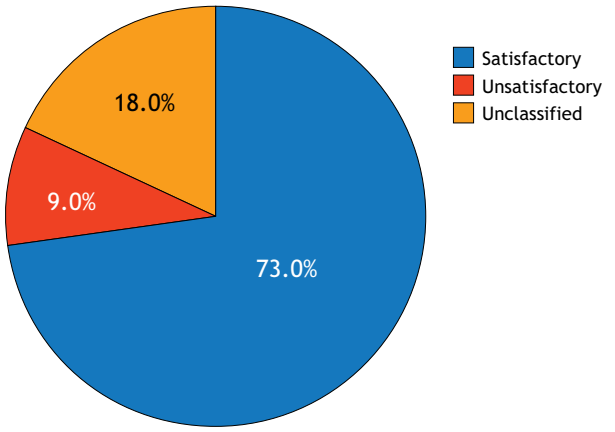
Among the actions, the import suspension is the most recurrent (26.5%), which is understandable, since most of the APIs used in Brazil are of foreign origin[4]. On the other hand, the suspension of exports occurred only once (0.7%), which can be explained by the low production of pharmochemicals in Brazil.

In general, it was observed that the year with the highest number of companies warned was also the year with the highest number of tax actions cited. In 2019, 16 companies were notified. In 2018, there were 14 companies and 12 companies in 2013. The year 2019, despite presenting two companies more than 2018, presented twice as many shares, which may represent greater rigor. The manufacture of API has increasingly attracted the attention of regulatory agencies, being the subject of discussion in public consultations on GMP and the qualification of supplier[28,46].

Eleven revocations were identified, eight of which were satisfactory, as they adequately meet the requirements of Anvisa and, in two, no information was found regarding their respective classifications, as shown in Figure 5. In 2016, the highest number of revocations was verified, that is, four (36.0%). In 2014 and 2019, there were no revocations. On the other hand, a revocation was observed for each remaining year.

Revocation is a process that allows the annulment of the tax action as long as the company rectifies the nonconformities notified by Anvisa. Although the majority of the revocations were satisfactory, only 11 (14.3%) of the total of 77 companies warned went through the revocation process. The data suggest that most companies have not undergone a new inspection to verify readjustment to regulation.

The year 2016 was highlighted in terms of the number of revocation actions, around 36.0%. However, no technical/scientific basis was found to justify the predominance in that year. On the



Source: Anvisa electronic portal, 2020.

Figure 5. Relative frequency of revocations related to the withdrawal of active pharmaceutical inputs presented by the Brazilian National Health Surveillance Agency in the years 2011 to 2019, in Brazil.

other hand, the absence of revocation in 2014 can be associated with the low number of notified companies, that is, three. In 2019, although there were the largest number of companies warned, none of them were cited for the revocation action.

The present study has limitations related to the lack of information or comparative studies related to inputs, with a predominance of studies on medicines. The data show that the predominance of irregular APIs occurs due to non-conformities in the GMP. However, in most cases, Anvisa does not indicate which specific item(s) of the current legislation regarding GMP were not complied with during the inspections. To fill this gap, it would be opportune to make the inspection report fully available on Anvisa's digital platform, as this information is relevant and of public interest. Although the inspection actions are mentioned, there is a lack of information regarding the parameters used to implement certain actions, which limited the discussion.

CONCLUSIONS

Most of the inputs present in Brazil were of foreign origin, since the import in the pharmochemical sector is more evident and there is a predominance of manufacturers located in China and India. Most of the companies warned in this analysis were identified, which demonstrates transparency and efficiency on the part of Anvisa.

The frequency of inspections was essential to detect irregularities in production, since the greater number of inspections influenced the amount of irregular APIs found. The therapeutic classes with the greatest predominance of withdrawn inputs were antimicrobials and antihypertensives.

The main reason for the withdrawal of API is the deficiency in GMP. However, Anvisa did not publish which specific items of current legislation the companies failed to comply with. On the other hand, Anvisa has credibility in developing regulatory standards, which are well illustrated. In addition, the inspection actions adopted are in line with the standards of international agencies such as FDA and EMA.

It is well known that Anvisa has been mobilizing itself to achieve excellence in national health control, with emphasis on the updating of resolutions, conducting debates in public consultations, and increasing the frequency and rigor of inspections in the pharmochemical industries.

Due to its originality, it is expected that this study will contribute to future publications and may serve as didactic material in the field of quality management applied to the production of API. Furthermore, it is noteworthy that academic works such as this, including teaching, research, and extension, contribute to the training of pharmaceutical professionals with a critical and multidisciplinary view, as well as to the empowerment of the population regarding the quality of API used in the manufacture of medicines in Brazil.

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Pinto NN, Resende KA - Acquisition, analysis, data interpretation, and writing of the work. Couto RO – Conception, planning (study design), 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.