**ORIGINAL ARTICLE**

# OVERVIEW OF ADVERSE EVENTS NOTIFICATIONS OF COMPOUNDED MEDICINES IN BRAZIL SINCE VIGIMED SYSTEM IMPLEMENTATION

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**Highlights:** (1) Pharmacovigilance of compounded drugs still in its incipient stages in Brazil. (2) Few adverse events of compounded drugs reported to VigiMed suggest underreporting. (3) More research on notification profiles and underreporting causes is vital.

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OVERVIEW OF ADVERSE EVENTS NOTIFICATIONS OF COMPOUNDED MEDICINES IN BRAZIL SINCE VIGIMED SYSTEM IMPLEMENTATION


## ABSTRACT

Introduction: Unfavorable occurrences during drug treatment are considered adverse events, important causes of hospitalization, morbidity and mortality. Pharmacovigilance is responsible for monitoring these events, but there are few records of its application in compounding pharmacies. Objective: The aim of the study was to identify and quantify adverse events reports of compounded drugs received by the VigiMed system, from December 2018 to December 2022. Method: A retrospective, descriptive and quantitative study using VigiMed records extracted from the Brazilian Open Data Portal. The analysis of notifications followed inclusion and exclusion criteria relevant to the topic. Results: Of the 67.109 notifications received by VigiMed in the period studied, 195 were suspected adverse events caused by compounded medicines, approximately 0,29% of the total. Heparin, silver nitrate and amiodarone were the active pharmaceutical ingredientes (API) with the highest absolute frequencies. API subjected to special sanitary control in Brazil were also identified: antidepressants, anxiolytics, anorexics and antiobesics. The most frequent route of administration was parenteral (94), followed by oral (50) and ophthalmic (25). Conclusions: The results allow us to conclude that there is a great diversity of active substances present in the reports, with the highest occurrence for componded medicines indicated for parenteral and oral use, consequently for a systemic effect, which requires greater care in preparation and vigilance in use. It was found that although pharmacists are the main notifiers of adverse events of compouded drugs, the practice of pharmacovigilance is poorly practiced or still in its incipient stages in Brazil.


**Keywords:** Pharmacovigilance; Compounded Medicines; Adverse events; VigiMed System.



## INTRODUCTION

According to the World Health Organization (WHO), any unfavorable occurrences during drug treatment are considered adverse drug events (ADE) and are important causes of hospitalization, morbidity and mortality[1].

To monitor the occurrence of these events there is pharmacovigilance, a set of activities related to the identification, evaluation, understanding and prevention of adverse effects or any problems related to the use of medicines[2,3].

Relevant issues for pharmacovigilance include ADE caused by deviations in the quality of medicines, therapeutic ineffectiveness, medication errors, the use of medicines for indications not approved in the health register (off-label use), the abuse of medicines, poisoning and events caused by drug interactions[2,3,4].

Spontaneous notification is the method most commonly used to carry out pharmacovigilance activities. It is carried out by filling in a standard form containing relevant data on the user, the drug and the ADE[3]. This form is available on the National Health Surveillance Notification System, a system used to report suspected adverse reaction associated with the use of products subjected to health surveillance in Brazil,[2,3].

Set up in 2009, the Notivisa system was responsible for receiving notifications related to suspected technical complaints and unwanted reactions following the use of medicines, health products, cosmetics, sanitizers, blood derivatives, among others. However, the system had inconsistencies due to a lack of integration with the WHO's monitoring systems[4,5].

As a result, in December 2018, the Notivisa system was replaced by VigiMed, the new management system for recording, processing and sharing adverse events specifically related to medicines and vaccines[4,5].

VigiMed is the adapted version of the VigiFlow system for Brazil, which is offered and monitored by WHO to the national pharmacovigilance centers of the member countries of the Programme for International Drug Monitoring (PIDM). However, technical complaints continue to be recorded in Notivisa, but those linked to ADE must be reported in VigiMed[4,5].

An industrialized drug is only commercialized after clinical trials have been carried out, through which various informations are obtained, including side effects, contraindications and potential adverse effects[6]. On the other hand, for a compounded medicine to be obtained, its composition must be included in a prescription from a qualified professional and health regulations state that this must contain details of its composition, pharmaceutical form (PF), dosage and method of use[6,7,8].

The compounding pharmacy offers various possibilities in terms of dose, quantity, form of presentation, combination of different substances and combination of different drugs in the same formulation[6,8]. According to Silva *et al.*[9], pharmaceutical excipients, used to confer stability, efficacy and even attractiveness, increase the possibility of this differentiated formulation to cause ADE to the patient.

Pharmacovigilance of compounded medicines varies significantly due to regulatory differences in different parts of the world. The European Medicines Agency (EMA) emphasizes the need for compounding pharmacies to adhere to Good Manufacturing Practice (GMP) standards and report ADE. However, the extent of ADE and the reporting of these events can differ between european countries, highlighting the need for a more harmonized regulatory framework[10,11].

In 2020, Portugal recorded two cases of cerebral venous thrombosis associated with the use of compounded weight-loss drugs, which resulted in serious adverse drug reactions (ADR), hospitalization and complications, even though these preparations were prescribed and dispensed in accordance with portuguese legislation[11]. Another study in Europe identified 12 case reports of lack of efficacy, ADE and medication errors associated with compounded drugs, which resulted in permanent sequelae[10].

In the United States of America (USA), during a routine inspection unrelated to compounded drugs, the Food and Drug Administration (FDA) found 4.202 records of ADE associated with compounded hormone pellets that had never been reported[12]. These events included possible associations with cancers, strokes and heart attacks, among others. Also in the USA, a survey identified more than 1.562 ADE, including at least 116 deaths, related to compounded drugs from 2001 to 2019[13]. FDA emphasizes the need for a more robust and vigilant approach, as well as the challenge of improving the reporting of compounded drugs ADE[12,14].

In Brazil, pharmacovigilance is mandatory for drug registration holders (RDC 406/2020)[2] and pharmacists (Law 13.021/14)[15]. Within the scope of the compounding pharmacy, RDC 67/2007[8] establishes among the duties and responsibilities of the pharmacist that any deviations in the quality of pharmaceutical supplies, occurrence of ADR and/or unforeseen drug interactions must be notified to the health authorities.

Pharmacovigilance is an important tool for improving drug safety [3,16]. Given the high impact of compounding pharmacies on the Brazilian drug market[17] and the unprecedented nature of many magistral preparations, especially those with drug combinations that have never been described before[6], it is of explicit relevance that post-marketing surveillance of compounded drugs be carried out, as well as the notification of ADE.

However, the scarcity of published studies about reporting compounded drug ADE suggests that pharmacovigilance in the magistral segment faces difficulties in its application,

possibly due to the less rigorous health regulations in relation to compounding pharmacies, or even due to conflicts of interest related to the connections between prescribers, dispensers and drug producers, in addition to the lack of security and motivation of health professionals to carry out the reporting[18].

Therefore, this study aims to determine the overview of notifications of compounded ADE received by the current national notification system, VigiMed, from its implementation until the year 2022.

## METHODS

This retrospective, descriptive study, with a quantitative approach, was carried out by surveying and analyzing the information contained in the open database of the VigiMed system, which receives reports of adverse events of medicines and vacines.

The data for this study were extracted from the Brazilian Open Data Portal (https://dados.gov.br/dados/conjuntos-dados/notificacoes-em-farmacovigilancia), according to the guidance of the National Health Surveillance Agency (Anvisa) after contact through the Anvisa Portal (https://www.gov.br/anvisa/pt-br/canais_atendimento/formulario-eletronico).

The data was available as reports of the notifications, in three Microsoft Office Excel® spreadsheets, one with general data, one with data about the medicines and one with data about the reactions. In the spreadsheets, the rows corresponded to each notification obtained from the VigiMed system, identified by a number in the format “BR-ANVISA-000000000”, and the columns corresponded to the variables.

For proper exploration, the data from the three spreadsheets was combined and duplicate variables removed, resulting in one spreadsheet. The variables of interest were analyzed using Epiinfo 7.2.5.0 (Centers for Disease Control and Prevention - CDC, Atlanta) and Microsoft Office Excel®.

The variables explored in the notification reports were: federative unit (FU) where the event occurred, date of notification, notifying group, company that holds the registration of the suspect drug, drug/event relationship, name of the suspect drug coded in WHODrug, active pharmaceutical ingredient (API) of the suspect drug coded in WHODrug, additional problems related to the drug, pharmaceutical form (PF) of the suspect drug, route of administration of the suspect drug and ADR or ADE coded in MedDRA according to system organ classes groups (SOC)

WHODrug is a global dictionary of medicinal information managed by the Uppsala Monitoring Center (UMC), WHO's collaborating center for international drug monitoring. It covers medicinal products and API, such as: active chemical substances, biopharmaceuticals, vaccines, dietary supplements, herbal medicines, radiopharmaceuticals and diagnostic agents. It is used by pharmaceutical companies and regulatory authorities to identify medicines in pharmacovigilance actions, such as ADR reports, and in clinical trials. Its application contributes to the accurate and standardized dissemination of information on medicines worldwide, facilitating an efficient data sharing[19,20].

The inclusion criteria used in the study were: notifications that occurred in the period after the implementation of the VigiMed system (December 10, 2018) until December 31, 2022, and notifications whose drug attributed as suspected of causing ADE had a compounding pharmacy as the holder of the registration.

The exclusion criteria used in the study were: notifications outside the specified period (December 10, 2018 to December 31, 2022), notifications with blank "DATA_NOTIFICATION" and "PRINCIPIOS_ATIVOS_WHODRUG" fields, API from compounding pharmacies not reported as suspected of causing the event, API reported as suspected of causing the event whose origin could not be identified as from a compounding pharmacy and API with blank "DETENTOR_REGISTRY" field.

In order to begin applying the inclusion and exclusion criteria, it was necessary to analyze the variable "REGISTRATION_HOLDER" (the company that holds the registration for the suspect drug) of each notification in isolation, in order to identify reports referring to compounded drugs.

After individual data analysis, the total number of notifications regarding compounded drugs reported to the VigiMed system from December 10, 2018 to December 31, 2022 was obtained, a period determined by the transition from the Notivisa system to the VigiMed system.

The notifications resulting from this first treatment were allocated to a spreadsheet called "Notifications of Compounded Medicines". Then, the spreadsheet was exported to the Epiinfo 7.2.5.0 software, where the frequencies, isolated and joint, of the variables of interest were calculated and analyzed. The summary of the results obtained is presented below, in the form of graphs and tables.

The present study is based on unnamed secondary data of events available in the Anvisa open database and according to resolution of the National Health Council (CNS) n.º 466/2012, it was not necessary to submit it to the Ethics Committee in Search (CEP).

## RESULTS

The research identified that 67.109 notifications of adverse events of drugs and vaccines were received by the VigiMed system between December 10, 2018 and December 31, 2022.

After applying the defined criteria, processing and data analisys, 195 ADE reports were identified from compounding pharmacies, whose API was suspected of causing the ADE, representing approximately 0,29% of the total number of reports at the described period.

The distribution of the time series presented an annual average of 39 notifications, a standard deviation of 27,89 and a coefficient of variation of 71,52%. In 2018, only one notification was identified (0,51%). In 2019, 35 notifications (17,95%), an increase of 3.400% compared to the previous year. In 2020, 72 notifications (36,92%), an increase of 106% compared to the previous year. In 2021, 69 notifications (35,38%), a 4% reduction compared to the previous year. In 2022, 18 notifications (9,23%), a 74% reduction compared to the previous year (Table 1).

Despite the high number of notifications without information about the federative unit of origin (104 notifications, equivalent to 53,33%), through analysis of the general overview it was possible to determine the absolute and relative frequencies of notifications of ADE handled by brazilian state (Table 1).

The most frequent states were São Paulo with 24 notifications (12,31%), Ceará with 15 notifications (7,69%), Minas Gerais with 14 notifications (7,18%) and Bahia with 9 notifications (4,62%). The states of Espírito Santo, Goiás, Maranhão and Pará were less frequent, with one notification each (0,51%) (Table 1).

The analyzed data showed that during the studied period, pharmacists were the main notifiers of compounded drugs ADE, with 156 notifications (80,00%), followed by “other health professionals” with 19 notifications (9,74%), “consumers or other non-health professionals” with 15 notifications (7,69%), physicians with four notifications (2,05%) and lawyers with one notification (0,51%) (Table 1).

Regarding the types of ADE identified in the notifications, it was found that the majority of these were suspected ADR (187 notifications, equivalent to 95,90%), followed by

four “medication error” (2,05%), three “off-label use” (1,54%) and one “quality deviation” (0,51%) (Table 1).

Table 1. Profile of notifications of suspected ADE involving compounded drugs from December 10, 2018 to December 31, 2022, in Brazil, according to federative unit (FU) of origin, year, notifier and type of ADE. (N=195).

| | n | % |
|---|---|---|
| **Year** | | |
| 2018 | 1 | 0,51% |
| 2019 | 35 | 17,95% |
| 2020 | 72 | 36,92% |
| 2021 | 69 | 35,38% |
| 2022 | 18 | 9,23% |
| **FU of report origin** | | |
| Not informed | 104 | 53,33% |
| SP | 24 | 12,31% |
| CE | 15 | 7,69% |
| MG | 14 | 7,18% |
| BA | 9 | 4,62% |
| RN | 6 | 3,08% |
| SC | 6 | 3,08% |
| RJ | 4 | 2,05% |
| RS | 4 | 2,05% |
| DF | 3 | 1,54% |
| PR | 2 | 1,03% |
| ES | 1 | 0,51% |
| GO | 1 | 0,51% |
| MA | 1 | 0,51% |
| PA | 1 | 0,51% |
| **Notifier** | | |
| Pharmacist | 156 | 80,00% |
| Other health professionals | 19 | 9,74% |
| Consumer or other non-health professional | 15 | 7,69% |
| Physician | 4 | 2,05% |
| Lawyer | 1 | 0,51% |
| **Type of ADE** | | |
| Adverse reaction | 187 | 95,90% |
| Medication error | 4 | 2,05% |
| Off-label use | 3 | 1,54% |
| Quality deviation | 1 | 0,51% |

Source: Pharmacovigilance notifications (Anvisa/VigiMed); Elaborated by the authors, 2023.

After identification and analysis of the API present in the notifications, it was observed that the majority are of a chemical-synthetic origin. There was also a higher number of API reports (N=206) than the number of notifications (N = 195), considering that some notifications presented more than one API suspected of producing the ADE. Table 2 presents the 74 API and their absolute (n) and relative frequencies (%).

Table 2. Absolute (n) and relative (%) frequency of API, coded in WHODrug, suspected of causing ADE, reported to VigiMed from December 2018 to December 2022, in Brazil (N = 206).

| API | n | % | API | n | % |
|---|---|---|---|---|---|
| Heparin | 29 | 14,08% | Cetirizine hydrochloride | 1 | 0,49% |
| Silver nitrate | 20 | 9,71% | Chloroquine phosphate | 1 | 0,49% |
| Amiodarone | 13 | 6,31% | Chorionic gonadotrophin | 1 | 0,49% |
| Magnesium sulfate | 11 | 5,34% | Cisplatin | 1 | 0,49% |
| Caffeine | 8 | 3,88% | Clomifene citrate | 1 | 0,49% |
| Dipyridamole | 7 | 3,40% | Clonazepam | 1 | 0,49% |
| Polidocanol | 7 | 3,40% | Cytarabine | 1 | 0,49% |
| Fluorescein | 6 | 2,91% | Dapsone | 1 | 0,49% |
| Hyaluronidase | 6 | 2,91% | D-mannose\|Vaccinium macrocarpon | 1 | 0,49% |
| Phytomenadione | 6 | 2,91% | Famotidine | 1 | 0,49% |
| Patent blue | 4 | 1,94% | Finasteride | 1 | 0,49% |
| Alprostadil | 3 | 1,46% | Fluoxetine | 1 | 0,49% |
| Furosemide | 3 | 1,46% | Gabapentin | 1 | 0,49% |
| Ganciclovir sodium | 3 | 1,46% | Garcinia gummi-gutta | 1 | 0,49% |
| Glucose | 3 | 1,46% | Glucosamine | 1 | 0,49% |
| Hyoscine | 3 | 1,46% | Griseofulvin | 1 | 0,49% |
| Methylthioninium chloride | 3 | 1,46% | Harpagophytum procumbens | 1 | 0,49% |
| Potassium chloride | 3 | 1,46% | Indometacin | 1 | 0,49% |
| Povidone-iodine | 3 | 1,46% | Ivermectin | 1 | 0,49% |
| Vitamins nos | 3 | 1,46% | Magnesium chloride | 1 | 0,49% |
| Bupropion | 2 | 0,97% | Menadione | 1 | 0,49% |
| Duloxetine | 2 | 0,97% | Metamizole sodium | 1 | 0,49% |
| Ergocalciferol | 2 | 0,97% | Methotrexate sodium | 1 | 0,49% |
| Hydroxychloroquine | 2 | 0,97% | Minoxidil | 1 | 0,49% |
| Omeprazole | 2 | 0,97% | Naltrexone | 1 | 0,49% |
| Potassium phosphate dibasic | 2 | 0,97% | Paclitaxel | 1 | 0,49% |
| Propantheline bromide | 2 | 0,97% | Petrolatum | 1 | 0,49% |
| Spironolactone | 2 | 0,97% | Phlebodium aureum | 1 | 0,49% |
| Alprostadil\|Papaverine\|Phentolamine | 1 | 0,49% | Rituximab | 1 | 0,49% |
| Amfepramone | 1 | 0,49% | Sibutramine | 1 | 0,49% |
| Amorolfine | 1 | 0,49% | Silver protein | 1 | 0,49% |
| Anastrozole | 1 | 0,49% | Simvastatin | 1 | 0,49% |
| Ascorbic acid | 1 | 0,49% | Tacrolimus | 1 | 0,49% |
| Azacitidine | 1 | 0,49% | Tadalafil | 1 | 0,49% |
| Calcium chloride | 1 | 0,49% | Testosterone | 1 | 0,49% |
| Calcium folinate | 1 | 0,49% | Topiramate | 1 | 0,49% |
| Captopril | 1 | 0,49% | Tranexamic acid | 1 | 0,49% |
| **Total** | | | | **206** | **100,00%** |

Source: Pharmacovigilance notifications (Anvisa/VigiMed); Elaborated by the authors, 2023.

The presence of API on the list of medicines under special control in Brazil[21], which are restricted for prescription and sale, was verified: antidepressants (bupropion and fluoxetine); anxiolytics (clonazepam); anorexics (amfepramone) and antiobesics (sibutramine).

The 10 API with the highest frequencies were: *heparin* (14,08%); *silver nitrate* (9,71%), *amiodarone* (6,31%), *magnesium sulfate* (5,34%), *caffeine* (3,88%), *dipyridamole* (3,40%), *polidocanol* (3,40%), *fluorescein* (2,91%), *hialuronidase* (2,91%) e *phytomenadione* (2,91%).

Figure 1 shows the distribution of API stratified by pharmaceutical form (PF) and route of administration. There were limitations to this analysis, since the "pharmaceutical form" had a large number of uninformed fields (125). However, it was possible to observe that parenteral solution (41) and ophthalmic solution (24) were the most frequent. The most frequent routes of administration were parenteral (94), oral (50) and ophthalmic (25). This result indicates a higher occurrence of compounded medicines in injectable form, which require greater care in their preparation and use.

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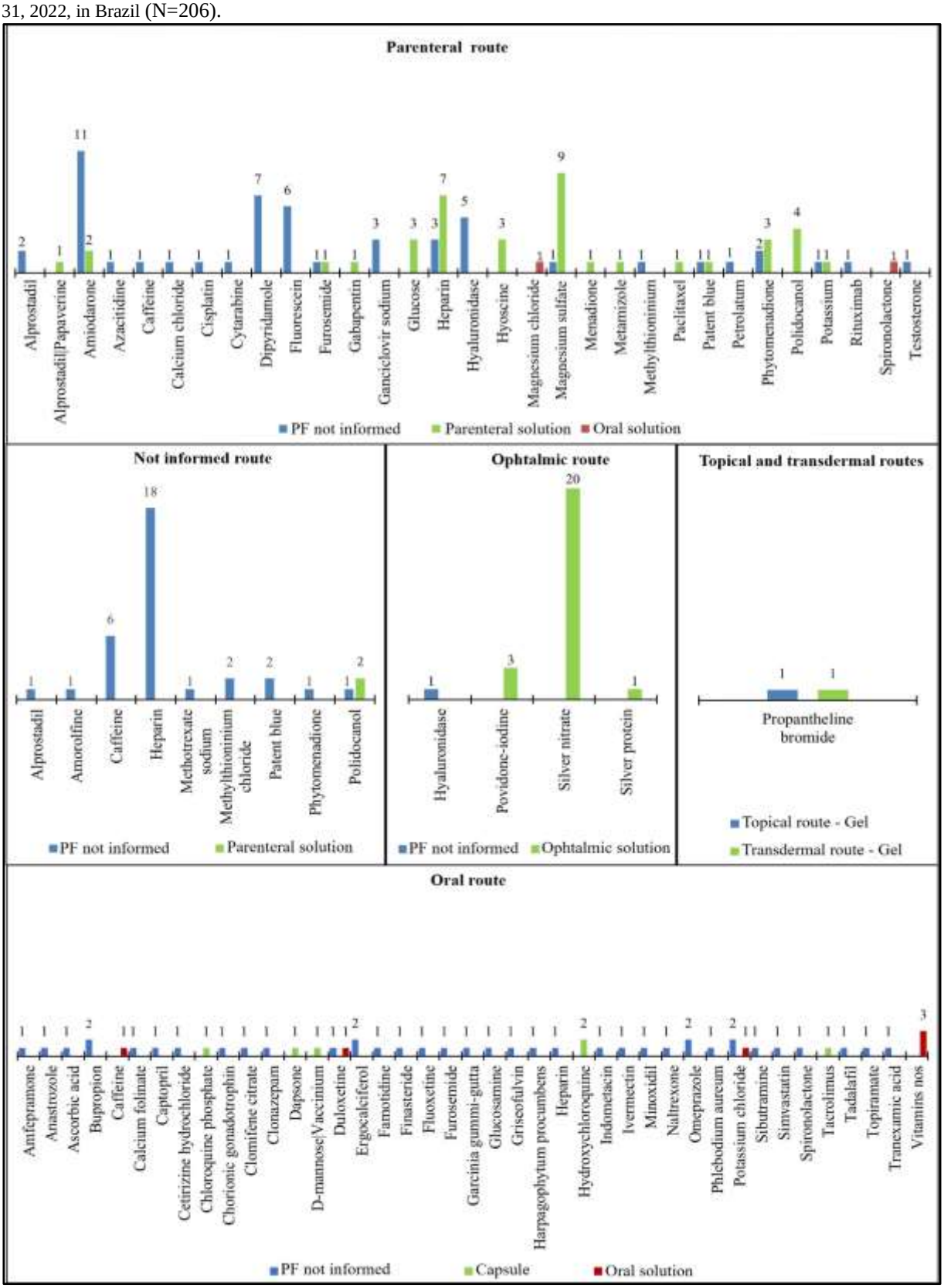
Figure 1 Distribution of absolute frequencies of API, according to pharmaceutical form and route of administration, identified in the 195 notifications of adverse events to compounded drugs reported to VigiMed from December 10, 2018 to December 31, 2022, in Brazil (N=206).




Source: Pharmacovigilance notifications (Anvisa/VigiMed); Elaborated by the authors, 2023.

Just as each notification can present more than one API, the same is true for suspected ADR. There were 392 reports of ADR indentified in the 195 notifications of adverse events to compounded drugs, an average of approximately two ADR per notification.

In VigiMed, ADR are classified under the terminology MedDRA (Medical Dictionary for Regulatory Activities), whose main feature is the hierarchical division of API into five levels. In this study, were analyzed the most extensive classification, the SOC classification (System Organ Classes) of the 392 ADR reports identified.

Figure 2 shows the distribution of absolute frequencies (n) of the 14 API with the highest number of ADR reported ($n \geq 9$), stratified by SOC classification. The SOC with the highest frequencies, according to the site of ADR manifestation, were: nervous system disorders (35), eye disorders (26), general disorders and clinical conditions at the site of administration (25), gastrointestinal disorders (25), vascular disorders (23), disorders of the skin and subcutaneous *t*issues (17), respiratory, thoracic and mediastinal disorders (15), disorders of the hematological and lymphatic systems (10), metabolic and nutritional disorders (9) and investigations (9).

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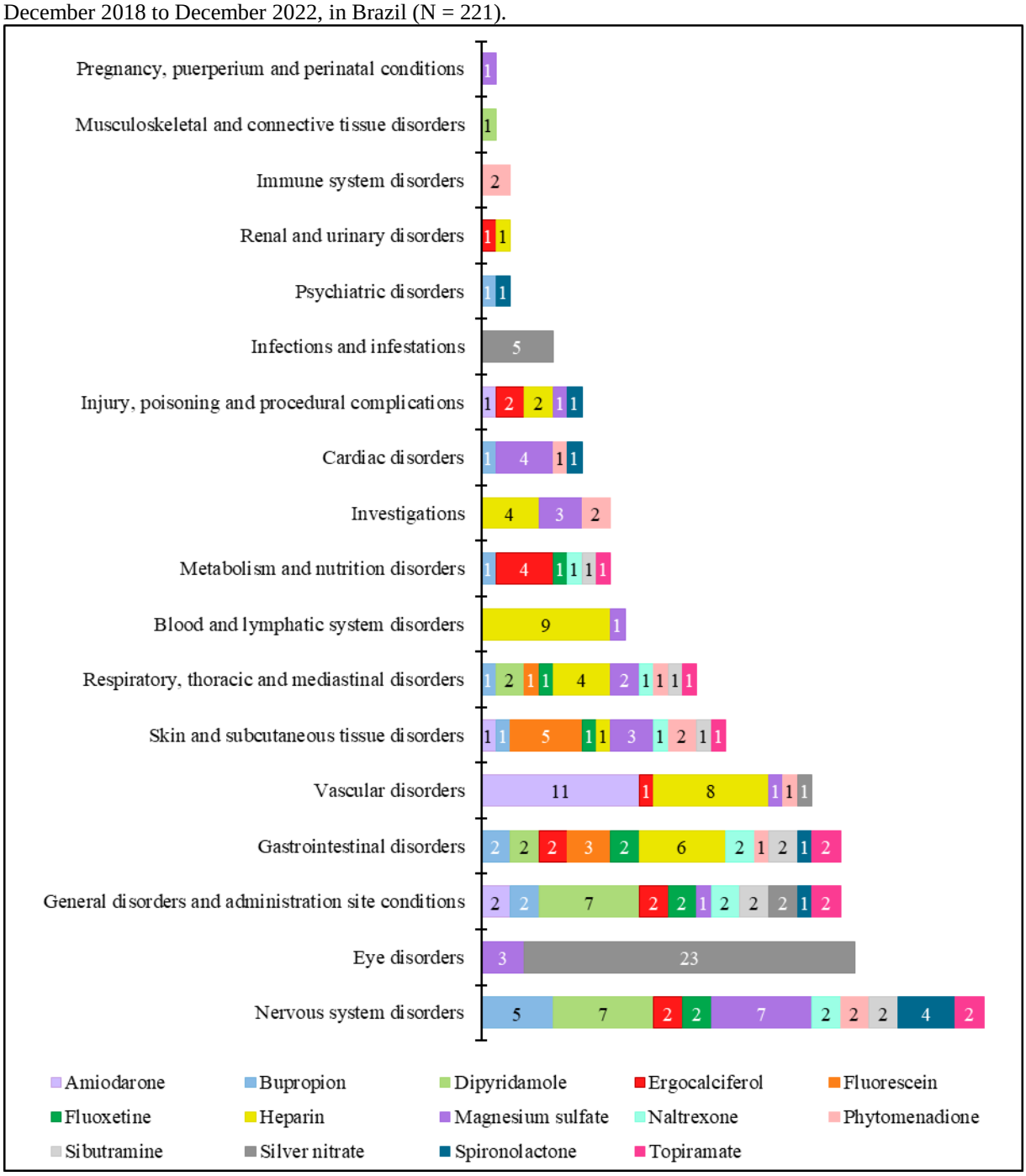
Figure 2. Joint distribution of the absolute frequencies of the 14 API of compounded medicines with the highest number of ADR reports classified according to SOC, identified in the 195 notifications reported to VigiMed from December 2018 to December 2022, in Brazil (N = 221).




Source: Pharmacovigilance notifications (Anvisa/VigiMed); Elaborated by the authors, 2023.

## DISCUSSION

The speed that changes in epidemiological patterns are being observed shows the importance of having tools that promote the correct understanding of health information[22]. VigiMed is a Health Information System (HIS) that monitors adverse events to medicines and vaccines, contributing to the production of knowledge and for the definition of health problems and risks[4].

The standard deviation of 28,05 (coefficient of variation 72,28%) referring to the annual average of notifications identified in this study, indicates considerable heterogeneity that can be attributed both to the low number of notifications at the beginning of the period, since it was only December 2018 (launch of the VigiMed system), and to the reduction in the number of notifications at the end of 2022.

The low percentage of notifications of adverse events to compounded medicines, 0,29% of the total number of notifications from 2018 to 2022, is alarming, mainly due to the unprecedented nature of many magistral preparations, and it is possible to infer that the number of underreporting is high and could probably hide the occurrence of health problems[18, 23-27].

A study in India[23], carried out with community pharmacy pharmacists, found that most of these professionals reported difficulty in identifying and reporting any ADR due to their low level of clinical knowledge.

Another study[24], carried out in Saudi Arabia, found that the main factors discouraging hospital pharmacists from reporting ADR are: the absence of a professional environment to discuss an ADR, followed by insufficient knowledge of pharmacotherapy or lack of clinical knowledge, which is a significant barrier, constituting a major limiting factor for pharmacovigilance practice.

In Nigeria, a study[25] conducted among community pharmacists also stated that the incidences of ADR reporting are very rare, even though they have sufficient knowledge.

A study assessed the knowledge, attitude and practice of pharmacovigilance among health professionals in Brazil and found that although pharmacists have a good level of knowledge and practice in pharmacovigilance compared to doctors and nurses, their attitudes and behavior in the event of an ADE were considered poor[26].

In this context, several factors corroborate underreporting, such as the difficulty in recognizing a condition as an ADR, difficulty in clinical diagnosis, difficulty in attributing

causality to the drug, lack of time and difficulty in interpreting the terms used in pharmacovigilance.

Studies indicate that many health professionals only report cases in which a causal relationship has been observed, failing to report other cases. In many situations, both professionals and users are unaware of what to report, as they believe that only serious and rare ADR should be reported[18,27].

According to Anvisa's Report n.º 01/2019, which provides guidelines for reporting in the VigiMed system, any undesirable medical occurrences derived from the use of a medicine or vaccine must be reported, even if it is not certain that the occurrence is caused by the treatment[5].

Many professionals mention the fear of being punished for reporting, as well as the existence of conflicts of interest related to the connections between prescribers and pharmacy owners. It is necessary to change the negative and punitive image that has been attributed to the act of reporting, because the principles that govern pharmacovigilance actions, that is, the identification, evaluation and prevention of ADE, are based on the ethical commitment of health professionals and the actions carried out on drug safety are intended to improve health care[18,27,28].

The obligation that the pharmacist has to notify the health authority about any occurrences of ADR and/or unforeseen drug interactions, is probably related to the high number of notifications made by this professional, verified during the analysis of the data obtained in this study[8,15].

In the VigiMed system, each report can generate several related records, because not only is polypharmacy common, but the same drug can trigger more than one reaction. It is therefore possible for the same identification number to be linked to more than one record of medicine used and reactions identified[5,29].

In this study, relevant correlations were observed between the results obtained for API most reported as suspected of causing ADE, most reported clinical manifestations and the most frequent pharmaceutical forms and routes of administration.

The most frequent API in the reports, heparin is an anticoagulant used in the treatment and prophylaxis of thromboembolic conditions, such as venous thrombosis, pulmonary embolism, among others. However, its use presents a risk of developing disorders of the

hematological and lymphatic systems (thrombocytopenia), vascular disorders (hemorrhages) and gastrointestinal disorders (gastric and esophageal hemorrhages)[30].

The second most common API, silver nitrate is used in the prophylaxis of neonatal ophthalmia in the form of a 1% ophthalmic solution, but its use presents a risk of developing eye disorders such as chemical conjunctivitis[31].

The third most frequent API in the reports was amiodarone, an antiarrhythmic drug widely used intravenously to treat arrhythmias, atrial fibrillation, atrial flutter and refractory ventricular tachycardia. However, there is a high risk of developing vascular disorders during intravenous therapy, including phlebitis, inflammation along the vein that triggers platelet aggregation[30].

The parenteral route of administration was the most prevalent in all the reports, which includes the subcutaneous, intradermal, intramuscular, intravenous and intrathecal routes. This finding leads to the idea of higher associated risk, given that the invasiveness of this route promotes rapid distribution of the drug, which can be an aggravating factor for ADR, as well as making it difficult to reverse the condition[32].

Another risk in the injectable compounded medicines is the possibility of contamination during the compounding process, which would compromise the safety of the formulation. However, this risk can be mitigated by adopting appropriate safety measures, as provided for in the regulatory standards[8].

According to brazilian legislation[8], pharmacies are legally allowed to compound sterile drugs, as long as they comply with the requirements established to guarantee the quality, safety and efficacy of these products, set out in Annex IV of RDC n.º 67 of 2007 (Good Practices for Compounding Sterile Products), in addition to the inclusion of the activity in the Special Operating Authorization and in the Sanitary License.

The preparation of sterile medicines in a compounding pharmacy includes the reconstitution, transfer, incorporation and fractionation of any sterile medicine intended for use in health services[8], which covers and probably explains the prevalence of injectable medicines identified in this study.

During an analysis of the notifications, two drugs in the form of oral solutions (magnesium chloride and spironolactone) were identified as being administered through a parenteral route. This occurrence is highly relevant, since the parenteral route should only be

used for the administration of sterile pharmaceutical forms, which does not include oral solutions [33].

Several reports of quality deviations associated with compounded drugs can be found in the scientific literature. A study in Brazil analyzed the profile of compounded drug notifications and found a predominance of technical complaints[34,35]. In Europe, were found 12 case reports of lack of efficacy and medication errors associated with compounded drugs that resulted in permanent sequelae[10]. However, few studies address ADR associated with compounded drugs.

Researchers reported the occurrence of a suspected 4.202 reports of ADE associated with the use of compounded hormone pellets, recorded in a data file generated by an American company, none of which had been reported to the US FDA. This situation was verified during a routine inspection by FDA investigators. The events recorded in the reports had possible associations with cancers, including endometrial and prostate cancers, strokes, heart attacks, deep vein thrombosis, cellulitis and pellet extrusions[12].

This study deals with adverse reactions to compounded drugs, so the comparison of these results is also limited, given the small number of scientific publications specific to this approach.

Analysis of the data obtained in the present study verified that the most frequent ADR, according to the SOC classification, were: nervous system disorders associated with dipyridamole and magnesium sulphate; eye disorders, whose suspected causality was attributed to silver nitrate; vascular disorders with suspected causality attributed to heparin and amiodarone; general disorders of clinical conditions at the administration site associated to dipyridamole and amiodarone; vascular disorders with suspected causality attributed to heparin and amiodarone; general disorders and administration site conditions associated to dipyridamole; and blood and lymphatic system disorders with suspected causality attributed to heparin.

However, a descriptive study[36] of the reports notified to the brazilian pharmacovigilance system Notivisa between 2008 and 2013, which did not indicate whether they were compounded medications, verified that the most frequent ADR were part of the SOC related to skin conditions and related disorders. This study also found that neoplastic agents, immunomodulators and anti-infective drugs were the therapeutic classes most related to serious ADR.

Furthermore, another study[37] analyzed spontaneous reports of suspected ADR in children aged 0 to 12, notified by Anvisa between 2008 and 2013, and found that skin disorders and vomiting were the main reports of suspected ADR, with the skin being the most affected organ. According to the authors, this result may be related to the differences in children's physiology, which increases their predisposition to skin reactions.

Another extremely important limitation found in carrying out this study was the identification of the origin of the drug suspected of causing the ADE. In order to classify the notifications as coming from compounding pharmacies, were used the data reported in the "REGISTRATION_HOLDER" field of the form, as there is no other data that allows for the identification of the manufacturer of the drug. However, compounding pharmacies are not registration holders[8] and there is no currently function on the VigiMed system notification form to distinguish the origin of the suspected drug as compounded or industrial[38].

During the analysis of the notifications, were found data reported in the "REGISTRATION_HOLDER" field such as: "compounding", "magistral", "compounded pharmacy", "compounded", in addition to numbers referring to the batch of the compounded drug used, expressions such as "I don't know", in addition to many notifications with this field blank.

Therefore, it is possible to infer that there is a lack of knowledge among notifiers about how to fill the form correctly. The lack of correct information compromises the effectiveness of the assessment and investigation of ADE, hindering the efficacy of the expected pharmacovigilance actions.

## CONCLUSION

The results obtained in this study allow to conclude that the pharmacovigilance of compounded medicines is poorly practiced or still in its incipient stages in Brazil.

The VigiMed system is proving to be effective in speeding up the notification process, but in the current system form there is only one field to inform the origin of the suspect drug, called "registration holder", which does not include the notification of adverse events to compounded drugs. This way, the current form needs to be adapted so that the origin of the suspect drug can be notified correctly.

Despite the significant number of compounding pharmacies in Brazil, their important impact on the national medicines market and especially because of the nature of compounded drug formulations, the low number of adverse events to compounded drugs reported to VigiMed implies that there is a high number of underreporting. In addition, the many incomplete or incorrectly reports highlight the urgent need for training and dissemination of the importance of pharmacovigilance and how to carry it out.

The scarcity of publications about compounded medicines pharmacovigilance shows that this is a subject that is still poorly covered, despite the mandatory nature of its implementation. Therefore, further studies, such as characterizing the profile of notifications and investigating the reasons for underreporting, are extremely necessary.

A better understanding of the profile of notifications and problems related to the use of compounded medicines could support the development of strategies to ensure greater safety, minimize risks and possible damage to the health of users, as well as boosting the segment's growth and improve the quality of its medicines.

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