

Evolution and key elements of the Brazilian pharmacovigilance system: a scoping review beginning with the creation of the Brazilian Health Regulatory Agency

Evolução e elementos-chave do sistema de farmacovigilância do Brasil: uma revisão de escopo a partir da criação da Agência Nacional de Vigilância Sanitária

Evolución y elementos-clave del sistema de farmacovigilancia de Brasil: una revisión de alcance a partir de la creación de la Agencia Nacional de Vigilancia Sanitaria

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Abstract

This scoping review aims to describe and characterize the Brazilian pharmacovigilance system Brazil (SINAF) and verify to what extent it meets the minimum requirements proposed by the World Health Organization for the functional performance of this type of national system. The literature search strategy used STARLITE recommendations and search terms in MEDLINE/PubMed, Google, the Brazilian National Press, and the website of the Brazilian Health Regulatory Agency (Anvisa), from 1999, when Anvisa was created, to March 2016. The review included 47 publications (4.4%), out of a total of 1,068 identified, in the following order: 14 legal provisions (29.8%), 13 (27.6%) technical documents, and 10 (21.3%) scientific articles. The studies and technical documents covered the creation of the first pharmacovigilance technical unit at the federal level, the reporting system for adverse events, the National Monitoring Center, and the Technical Chambers on Medications. The reporting rate for adverse drug events in Brazil in 2013 was 36 reports per million inhabitants, considerably lower than the target proposed in the international literature, which suggests 300 reports per million inhabitants. This study identified structural and functional aspects that can compromise the performance of SINAF, such as lack of legislation officially establishing the system itself and its objectives.

Health Evaluation; Health Information Systems; Pharmacovigilance; Drug-Related Side Effects and Adverse Reactions; Adverse Drug Reaction Reporting Systems

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Introduction

A pharmacovigilance system is an essential part of drug regulatory policies¹ and pharmacogovernance, defined as government structures, policy instruments, regulations, standards, and institutional authority, administered in such a way as to safeguard society's interests in relation to patient safety, and to protect against adverse drug events (ADEs)². The purpose is to identify, evaluate, analyze, and prevent ADEs³, which are relevant causes of morbidity and mortality^{4,5,6}.

The World Health Organization (WHO) has encouraged the implementation of sustainable national pharmacovigilance systems^{1,7}, especially since the "thalidomide epidemic" in 1961-1962. Different approaches have characterized the studies analyzing public health surveillance systems^{8,9,10}, particularly pharmacovigilance systems^{1,11,12}. In 2010, the WHO issued recommendations for minimum requirements and attributions of the national pharmacovigilance systems¹³.

Brazil has a reasonably comprehensive legal framework for the country's pharmacovigilance activities. However, there is a persistent lack of studies evaluating pharmacovigilance activities, especially from the perspective of reporting systems and processing and analysis of the information and feedback to the reporting sources through effective actions that expand the rational use of medications and patient safety. The aim of this study was to describe and characterize Brazil's drug safety system, called the National Pharmacovigilance System (SINAF)^{14,15}, emphasizing the activities by the Brazilian Health Regulatory Agency (Anvisa) and verifying compliance with the minimum national requirements for pharmacovigilance proposed by the WHO¹³.

Method

The scoping review was conducted in April and May 2016. It describes the evolution of the SINAF and its key elements, based on a non-exhaustive list from the European Centre for Disease Prevention and Control⁹. The results of the review of the documental evidence were used to verify the extent to which SINAF meets the minimum requirements suggested by the WHO for characterization of a "functional" pharmacovigilance system¹³, including: (1) a national pharmacovigilance center; (2) a national spontaneous reporting system; (3) a national database or information system for data collection and storage; (4) a pharmacovigilance advisory committee; and (5) a communication strategy for pharmacovigilance activities¹³. For the current study's purposes, the term "minimum" and "functional" were interpreted as: what should be done, at least, to ensure the existence of a national pharmacovigilance system, capable of providing some guarantee of user safety¹³.

The scoping review aimed to identify information in the so-called "gray" scientific, technical, and legal literature and summarize it as a narrative describing the evolution of the SINAF and its key elements. The review provides for six phases^{16,17}, described next. Divergences and doubts were resolved by consensus among the authors.

Phase 1: identification of the research question

The review addressed the following research question: "What were the characteristics, at the federal level, of the SINAF and its key elements, from January 1, 1999, to March 31, 2016?". This period was chosen because the authors felt that it represents a time of key changes in pharmacovigilance practices influenced by the creation of the Anvisa, concluding in 2016 at the end of the study's search strategy and document analysis. SINAF was defined as a set of activities coordinated by Anvisa, capable of: detecting and reporting ADEs, case investigation, data collection, analysis, and interpretation, including the identification and monitoring of safety signals, feedback, and dissemination of results and answers through prevention and control activities.

Phase 2: identification of publications

The literature search strategy for identification of publications followed STARLITE recommendations (*Standards for Reporting Literature Searches*)¹⁸ (Box 1).

Box 1

STARLITE summary description of literature search.

S	Selective sampling strategy Aimed to identify scientific studies, theses, dissertations, books, technical and legal documents, etc. (hereinafter “publications”) on aspects that could describe and characterize the SINAF as part of a health surveillance system with the following specific limits.
T	Types of publications Any qualitative, quantitative, descriptive, and evaluative studies, laws, guidelines, lecture materials, website contents, etc.
A	Approaches Electronic database searches, citations in references, Internet searches, publications known to the authors, and empirical knowledge by key informants.
R	Range, years Publications identified starting with the year of creation of Anvisa (1999) until March 31, 2016, totaling just over 17 years.
L	Limits Publications in English, Portuguese, or Spanish and not including studies in animals.
I	Inclusion Publications that contributed to the description and characterization of SINAF as to evolution and key elements. Exclusion Publications referring to: (i) studies on pharmacotherapy; (ii) study on characterization of ADEs; (iii) studies of any kind on vaccines; and (iv) studies on drug policy and pharmaceutical care.
T	Terms (keywords – MeSH and DeCS) Brazil (MeSH), Pharmacovigilance (DeCS), Anvisa, National Health Surveillance Agency, Notivisa, Reporting System in Health Surveillance, Adverse drug reaction reporting systems (MeSH), Post-marketing drug surveillance (MeSH), Adverse drug event (MeSH), sentinel surveillance (MeSH and DeCS), adverse reaction (DeCS), health surveillance system (DeCS), National Pharmacovigilance System, medications (DeCS) and Technical Chamber on Medications.
E	Electronic data sources MEDLINE/PubMed, SciELO, LILACS via Virtual Health Library Portal (BVS), <i>Sistema de Información Esencial en Terapéutica y Salud</i> (SIETES), Brazilian National Press (<i>Diário Oficial da União/Federal Daily Register</i>), CAPES database of theses and dissertations/Ministry of Education, Google and Anvisa website.

ADEs: adverse drug events; Anvisa: Brazilian Health Regulatory Agency; Capes: Brazilian Graduate Studies Coordinating Board; DeCS: *Descritores em Ciências da Saúde*; LILACS: Literature in the Health Sciences in Latin America and the Caribbean; MeSH: Medical Subject Headings; SciELO: Scientific Electronic Library Online; SINAF: Brazilian National Pharmacovigilance System; STARLITE: Standards for Reporting Literature searches.

The searches were conducted in April 2016 with 15 search terms, in keeping with each data source, and the different combinations were defined by “trial-and-error” until reaching the desired final arrangement.

The search in MEDLINE/PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) used 11 search terms in English, covering 21 combinations plus the expression “not animal”. In the Brazilian National Press (<http://portal.imprensanacional.gov.br>), two terms were used: pharmacovigilance and technical chamber on medications. This data source, where each search result was done annually, was characterized as a document, while in the selection phase a document that may have yielded more than one result was included as one publication. In Google (<https://www.google.com>), the search used a single combination of terms in quotations marks (“pharmacovigilance” AND “Brazil”) and only the first 100 results (classified according to relevance by Google) were verified, and the resulting documents were included in the study’s set of publications.

In the Anvisa website (<http://portal.anvisa.gov.br/>), publications were identified without using search terms, given the limitation of the agency’s search system, focusing on documents contained on two webpages: (i) the pharmacovigilance technical area (<http://portal.anvisa.gov.br/farmacovigilancia>) and (ii) the National Reporting System for Health Surveillance (Notivisa; <http://portal.anvisa.gov.br/notivisa>).

Phase 3: selection of publications

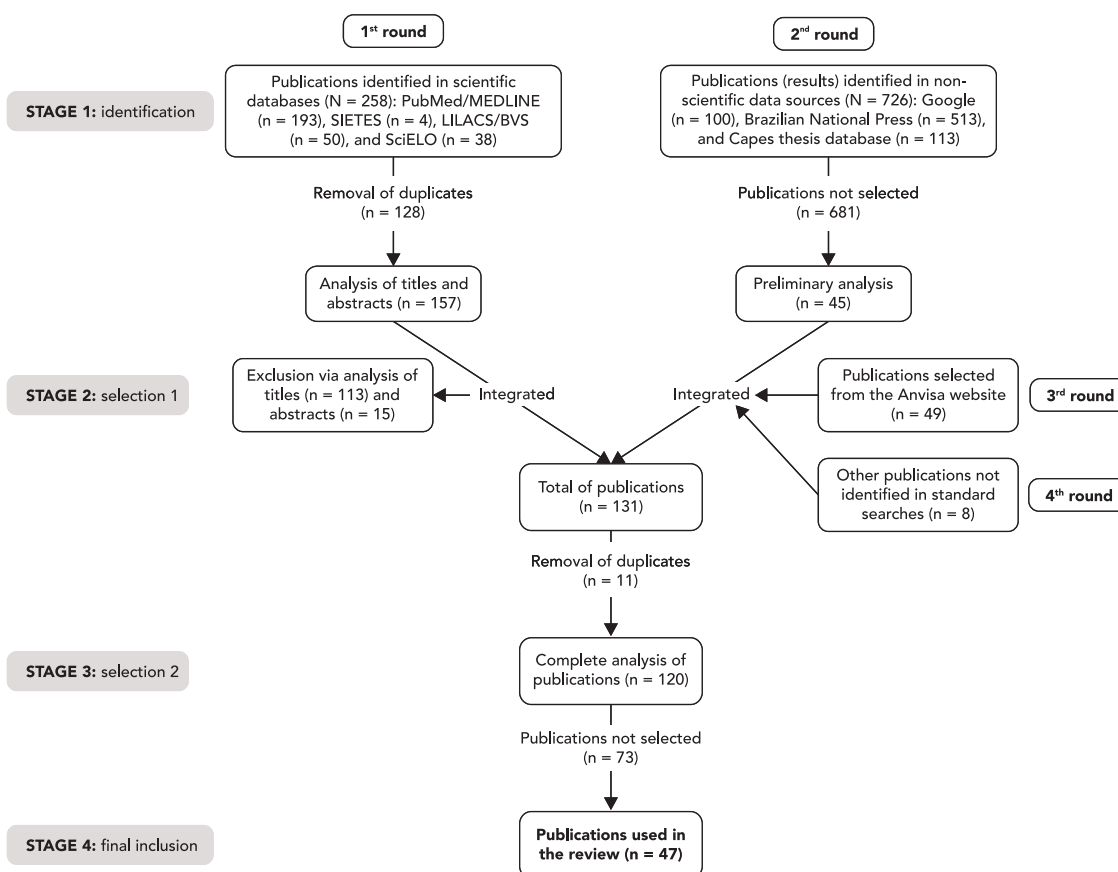
Based on the retrieved publications, one of the authors (D.M.M.) proceeded to the identification of those that were potentially eligible (Figure 1) according to the inclusion and exclusion criteria, indicating analysis of the full texts when necessary to confirm their relevance to the research question. The order in the choice of publications when the same topic appeared in different documents was: (i) first document published on the topic (primary document), in cases other than publication of scientific articles and (ii) scientific articles taking priority over congress proceedings, newsletters, bulletins, and others, in the absence of more current data. It was not possible to blind the reviewer in relation to any part of the publications.

Phases 4, 5, and 6: data extraction, analysis, and synthesis of publications and key informant's participation

Extraction of the qualitative evidence from the publications was based on a selective and iterative process, i.e., the authors alternated between reading the primary documents, extraction of the information, analysis, synthesis, and interpretation in various cycles based on the key themes ¹⁹. A

Figure 1

Flowchart of the selection process for publications in a scoping review: identification, selection, and final inclusion.



Anvisa: Brazilian Health Regulatory Agency; Capes: Brazilian Graduate Studies Coordinating Board; LILACS/BVS: Literature in the Health Sciences in Latin America and the Caribbean/Virtual Library of Health; SciELO: Scientific Electronic Library Online; SIETES: *Sistema de Información Esencial en Terapéutica y Salud*.

standardized summary spreadsheet was used for the data extraction, including the principal author, year, title, and/or other part of the content, type of document (scientific article, legislation, technical document, etc.) and data source.

The study also drew on the first author's empirical knowledge, having worked in the pharmacovigilance area of Anvisa from 2005 to 2010. The information from the staff expert referred to as the key informant is identified with the initials KI in the final text.

The study was approved by the Ethics Research Committee of Hospital de Clínicas de Porto Alegre, under case review n. 950.737/2015.

Results

Data from the scoping review

The search identified 1,068 publications, predominantly those characterized as “gray literature” in the identification (n = 783; 73.3%), selection 1 (n = 102; 77.8%), and final inclusion (n = 37; 78.7%) stages (Figure 1). The most frequent publications were, in the following order: legal provisions (n = 14; 29.8%), technical documents (n = 13; 27.6%), and scientific articles (n = 10; 21.3%). The main reasons for the rejection of 1,021 publications were: failure to meet inclusion criterion (n = 880; 86.2%) and duplicate publication (n = 139; 13.6%). In relation to the rejection of 128 scientific articles from the first round, the main reasons were: (i) studies on ADEs (n = 31; 24.2%); (ii) studies on vaccines (n = 21; 16.4%); and (iii) studies on drug treatment (n = 15; 11.7%).

Evolution of the configuration of the SINAF

Pharmacovigilance regulatory activities were effectively organized in Brazil beginning with the creation of Anvisa (*Law n. 9,782*²⁰, January 26, 1999), with the attributions, among others, of “*establishing and coordinating the toxicological and pharmacological surveillance systems*”. The year 1999 witnessed the creation of the first federal-level pharmacovigilance technical unit in the country, called the Pharmacovigilance Administration (GFARM), part of the General Drug Administration of the Directorate for Drugs and Products²¹.

According to the documents, the proceedings for the creation of the SINAF began in October 1999, with the compilation of the necessary documents for the National Pharmacovigilance Center, aimed at Brazil's adherence to the WHO Program for International Drug Monitoring²².

The method for spontaneous reporting for nationwide monitoring of ADEs was implemented for first time in 2000, through the reporting form on the Anvisa website²², basically covering adverse reactions and quality deviations in medications leading to patient harm, assessed and stored manually in a databank (“Bdfarm”)²³. That year, GFARM was renamed the Pharmacovigilance Unit (UFARM) (*Ruling n. 593*²⁴, August 25, 2000).

Some authors defended the participation of drug information centers or services (CIM/SIM) distributed across Brazilian states in the implementation of a National Pharmacovigilance System²⁵. Participation by UFARM representatives in the CIM/SIM Meeting in October 1999 and November 2000 produced cooperative proposals, aimed at the dissemination of the spontaneous reporting methods in health services²⁵, among other measures, as a way of publicizing the pharmacovigilance activities that were beginning under the coordination of Anvisa.

The year 2001 saw the creation of the National Drug Monitoring Center (CNMM), housed in the UFARM (*Ruling n. 696*²⁶, May 7, 2001), with the following responsibilities: (i) decentralize the collection and analysis of reports, training and supporting the state-level drug safety units for this purpose; (ii) develop a database and periodic analyses to assess rational and safe drug use and to generate signals and hypotheses; (iii) refer the ADE reports to the Uppsala Monitoring Centre (Uppsala, Sweden) on the WHO form; and (iv) disseminate the information to health professionals with alerts, bulletins, and reports, improving the clinical decision-making process and reporting²⁶.

The Technical Chamber on Medications (CATEME), created in 2001, established a roster of ad hoc consultants on medications^{27,28} with the following responsibility, among others: “*report on*

issues related to pharmacovigilance of medications...”²⁸. Also in 2001, Brazil became the 62nd member of the WHO Program for International Drug Monitoring, coordinated by the Uppsala Monitoring Centre^{22,29}, reaffirming the first pharmacovigilance activities by Anvisa. UFARM took charge of the implementation and coordination of SINAF, with provision for participation by Regional Pharmacovigilance Centers, “Sentinel Hospitals”, and “Sentinel Physicians”^{14,30}.

Some state-level health surveillance agencies have State Pharmacovigilance Centers, notably the states of São Paulo, Rio de Janeiro, Paraná, Santa Catarina, and Bahia^{2,31}. Several other states, like Ceará, implemented the Pharmacovigilance Center housed in Universidade Federal do Ceará since 1996, one of the most active in pharmacovigilance work in Brasil³².

The creation of the Sentinel Hospitals Project (currently called the Sentinel Network) by Anvisa in 2002 strengthened the organization of the SINAF. This was the first initiative by Anvisa to obtain information on the safety of drugs and other products, reaching a peak of 180 Brazilian hospitals³³.

The review identified a provision, which was soon revoked, proposing “sentinel physicians” to monitor and report clinical or laboratory events, treatment failures, or adverse drug reactions (ADRs)³⁴. The provision³⁴ defined a “sentinel physician” as a “*medical professional from a given specialty of interest to Anvisa who voluntarily agreed to the terms of the Sentinel Physicians project, contributing periodically with information on adverse reactions (safety), drug treatment results (effectiveness), and data on the use of health products selected for surveillance*”.

Brazil’s pharmacovigilance activities resulted in a 4,517% increase in spontaneous reports of suspected cases of ADRs analyzed by CNMM/UFARM from 2000 to 2004, or from 76 to 3,585 events, most of which from sentinel hospitals²².

In 2005, the spontaneous reporting method incorporated two forms of data collection in addition to the ADE reporting forms targeted to health professionals, namely: (i) reporting of adverse events by users of medications (Sisfarmaco)²³; and (ii) Reporting System for Adverse Events and Technical Complaints Related to Health Products (SINEPS), for sentinel hospitals²². That same year, Anvisa established the pilot project entitled Reporting by Pharmacies in the state of São Paulo, with initial participation by 43 pharmacies (out of a total of 14,000), aimed at increasing the number of qualified spontaneous reports of adverse events and quality deviations in medications^{2,22}. This was later expanded to other states of Brazil, with at least three changes: (i) the project’s name was changed to Reporting by Pharmacies Program; (ii) an advisory committee was created to support Anvisa in the Program’s development; and (iii) promotion of safe and rational drug use in the Community Pharmacy context³⁵.

In 2008, Anvisa created the Notivisa, providing for a standardized online form for data collection on drugs involved in health harms to patients (Notivisa-medicamento)^{2,23,36}. The system replaced the SINEPS and became the most wide-reaching alternative for reporting ADEs. Drug poisoning has a specific reporting form in Notivisa and its access focuses on centers for toxicological information and care (CIATs)³⁷. Although Notivisa-medicamento is Brazil’s main data repository on ADEs, there are still numerous reports from the state of São Paulo that are not integrated into the system. For these reports, Anvisa provides access via online spreadsheets (KI).

The document published by Anvisa in March 2008 entitled *Guidelines for Risk Management in Pharmacovigilance* describes SINAF as part of the National System for Reporting and Investigation (VIGIPOS), as a subsystem of the Brazilian Health Regulatory System (SNVS)¹⁵. The document harmonized definitions and work processes on risk management in pharmacovigilance with the SNVS, which involves Anvisa and state, municipal, and Federal District health surveillance agencies¹⁵.

Two legal provisions filled an important gap in the legal framework for consolidating the SINAF. *Resolution n. 4*³⁸ of February 10, 2009, ruled on pharmacovigilance activities by drug registration holders (DRM), such as mandatory reporting of adverse events, the creation of a minimum pharmacovigilance structure in the pharmaceutical laboratories, definition of adverse events to be reported to the SNVS, and health inspections of the pharmacovigilance activities conducted by the drug registration holders³⁸. *Resolution n. 36*³⁹ of July 25, 2013, determined patient safety measures in health services, requiring that such services report adverse events leading to death within 72 hours of the event. The improvements in SINAF contributed to a mean ADE reporting rate in Notivisa-medicamento from 2008 to 2013 of 25 per million inhabitants, ranging from 15 (2008) to 36 (2013)⁴⁰.

Description of key elements in the SINAF

• **Purpose and objectives**

The review failed to identify any document explicitly characterizing the purpose and objectives of SINAF. However, some of its important components, such as Notivisa-medicamento and CNMM, mention ends and objectives that can be attributed to the SINAF, aimed at orienting pharmacovigilance activities by the country's health surveillance authorities. The objectives of Notivisa-medicamento are: (i) to support SNVS in identification of adverse reactions or unwanted effects; (ii) to improve knowledge on the effects of products, and when indicated, alter the recommendations on their use and safety precautions; and (iii) to promote measures to protect the public health through regulation of products marketed in the country⁴¹. The principal objective of the CNMM is "*the early identification of a new adverse reaction or an increase in the knowledge of an adverse reaction with limited accumulated information and that may bear a causal relationship to the marketed drugs*"²⁶.

• **List of adverse events for reporting**

The list of ADEs was identified in ruling on holders of drug registrations, which could be extended to other reporting sources. The complete list includes: (i) suspected adverse drug reactions; (ii) adverse events due to deviations in drug quality; (iii) adverse events resulting from unapproved use of medications; (iv) drug-drug interactions; (v) total or partial therapeutic ineffectiveness; (vi) drug-related poisoning; (vii) abusive use of medications; and (viii) potential and actual medication errors^{42,43}. At the start of pharmacovigilance activities in Brazil, only ADRs and deviations in drug quality involving patient harms were reported to Anvisa.

• **Case definition**

No standard case definition for adverse events subject to surveillance was found in the search, according to health surveillance standards, which includes clinical manifestations, laboratory results, epidemiological information, and/or specific behaviors, as well as levels of case certainty, such as confirmed/defined, probable, possible, or suspected⁴⁴. Various Anvisa documents orient the reporting of "suspected" ADRs. The other levels of certainty are only used in the evaluation of causality for each adverse drug reaction¹⁵. Here, the categories of causality defined by the WHO and used by SINAF are the following: (i) defined; (ii) probable; (iii) possible; (iv) improbable; (v) conditional/not classified; and (vi) not accessible /not classifiable^{15,45}.

In the document *Guidelines for Risk Management in Pharmacovigilance*, Anvisa mentions the need to "*reassess causality and revise case definition based on new data*" in investigation in pharmacovigilance¹⁵.

• **Reporting sources**

It is possible for various reporting sources to record ADEs in different ways, especially in the Notivisa-medicamento system. These sources include independent health professionals such as physicians, pharmacists, and nurses, health surveillance professionals and/or staff affiliated with the Sentinel Network hospitals or Patient Safety Center (NSP), and other hospitals, sentinel physicians, reporting pharmacies, DRM, CIATs, universities, and individual citizens, patients, or family members (laypersons)^{34,36,46,47}. The latter can report events on a specific form, not integrated electronically into the Notivisa-medicamento system and available on the Anvisa website³⁶.

This diversity of reporting sources notwithstanding, four sources merit special attention in the following order, due to the volume of reports recorded in the Notivisa-medicamento system from 2008 to 2014: (i) professionals from the Sentinel Network/NSP; (ii) independent health professionals; (iii) professionals from other hospitals/NSP; and (iv) health surveillance professionals⁴⁶. During this same period, no reports came from either the Reporting by Pharmacies Program or the Sentinel Physicians⁴⁶.

- **Data and information flow**

Figure 2 shows an attempt at mapping the data flow for ADEs reported to SINAF. Given the different reporting sources, the flow shows at least three routes that converge in Anvisa, with some relevant cases of ADRs forwarded to the WHO Uppsala Monitoring Centre ²⁶.

As for the route that involves reporting to Notivisa-medicamento, each registered reporting source can monitor the set of its reports recorded in the system, the data of which are forwarded to Anvisa in real time. The capacity to manage and analyze the data with municipal, state, and national repercussions and the publication of information are the responsibility of the respective health authorities at their various management levels (KI). Information on ADEs reported by individual citizens, patients, and family members also reach Anvisa through the agency's hotline and its Ombudsman's Office (Figure 2) ⁴⁸.

- **Surveillance networks**

The networks for ADE surveillance consist of all the actors participating in the reporting process to Anvisa (KI), such as state, regional, municipal, and Federal District health surveillance agencies and the Sentinel Network. According to the purposes and objectives of SINAF, the pharmacovigilance technical area of Anvisa induced the establishment of surveillance networks within Brazil and abroad ^{49,50}, allowing an increase in the detection of adverse events, communication of alerts, and staff training ¹⁴. The initiatives for integration of SINAF with public health programs from other systems, like the National TB Control Program ⁵¹ and the National Program for the Prevention and Control of Viral Hepatitis ⁵² are examples of networks that have promoted ADE reporting in Brazil.

- **Population under surveillance and geographic coverage**

The target population basically includes residents of Brazil that have suffered health harms purportedly caused by medications licensed in the country (KI). Except for pregnant women, the review did not identify surveillance priorities as to vulnerable populations such as under-five children, elderly, and patients with multiple comorbidities ^{38,49,50}. The drugs under surveillance include phytomedicines, pharmacy-manipulated products, homeopathic preparations, specific products such as parenteral solutions and vitamins, over-the-counter drugs, and drugs prescribed by qualified health professionals ⁵³. Drug registration holders are required to send periodic safety reports to Anvisa on new drugs marketed in the country ³⁸.

There is mention of so-called "special-interest" adverse events such as agranulocytosis, anaphylaxis, aplastic anemia, blindness, malignant hyperthermia, toxic epidermal necrolysis, rhabdomyolysis, and Stevens-Johnson syndrome ¹⁵. However, it is not clear whether they are prioritized in the reporting flows.

The geographic coverage of SINAF includes the entire country, although some network strategies thus far do not cover all 27 states, like the State Pharmacovigilance Centers ³¹ and the Reporting by Pharmacies ⁵⁴. Others have not even been implemented at all, like the Sentinel Physicians program (KI).

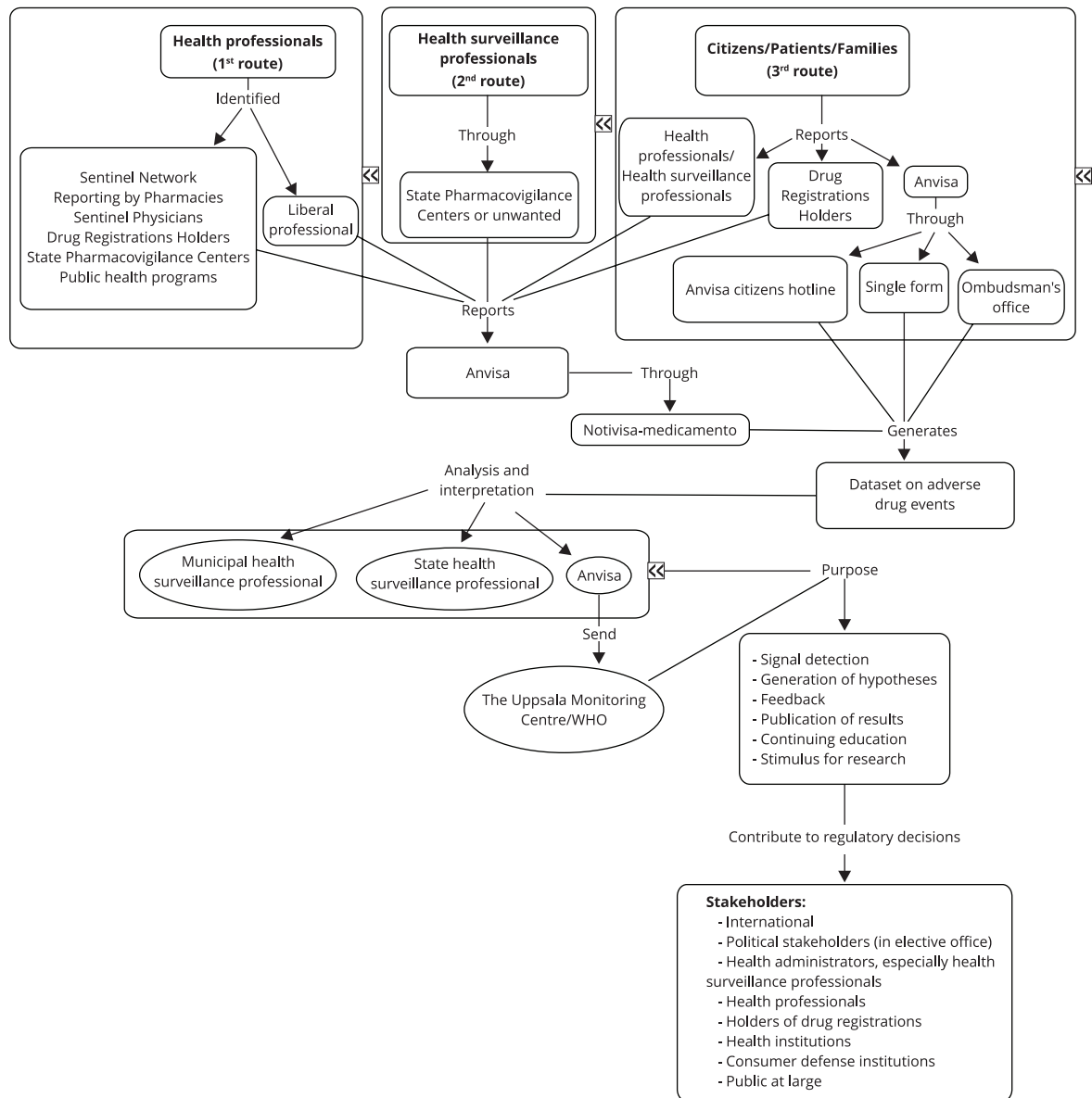
- **Types of surveillance**

SINAF is characterized as a passive surveillance system in which spontaneous reporting is the main method for monitoring ADEs (KI). Active surveillance has largely occurred to meet specific demands, as in the case of the abusive use of benzydamine, in which consultations are made with reporting pharmacies and CIATs as an alternative used by authors to explore this type of ADE ⁵⁵.

The other types of surveillance are: (i) mandatory – DRM and health services are required to report ADEs that have come to their attention and (ii) comprehensive – various documents published by Anvisa state that all deaths and other serious drug-related events must be reported, as well as all adverse reactions not listed on the product's package insert ^{39,41,56}.

Figure 2

Data and information flow on adverse drug events reported to the Brazilian National Pharmacovigilance System (SINAF).



Anvisa: Brazilian Health Regulatory Agency; WHO: World Health Organization.

• Reporting format and data specification

SINAF maintains and encourages the use of only online formats for the ADE reporting forms (citizens/patients/families and Notivisa-medicamento) ³⁶. Such forms record individual information related to ADEs, such as name, age, sex, medical diagnosis, description of the adverse event, date of onset and end of the event, currently used medications, time using the product, relevant complementary data, and reporting source, etc. ^{53,57}. The Notivisa-medicamento form for health professionals assessed in November 27, 2015, has at least 92 variables, covering four domains (KI): event, drugs/

company, patient or user, and other information⁵³. The content of the information on the individuals' identity is confidential.

- **Reporting rate**

The reporting rate was defined for holders of drug registrations and health services according to health standards. In the first case, every serious adverse event involving death or risk of death must be reported to Anvisa within seven days from receiving the information. The deadline is extended to 15 days for other serious adverse events³⁸. As for health services, the reports are to be sent monthly to Anvisa, and as mentioned previously, adverse events evolving to death must be reported within 72 hours of the event³⁹.

- **Data entry**

Data entry in Notivisa-medicamento requires using the user registration system, which allows different levels of access according to the user profile⁵³. Registered health surveillance professionals have access to the Notivisa-medicamento features that are not available to users registered as independent health professionals. The system validates the registered user's data before starting a new report. Information on ADEs are keyed manually into a data entry mask on the webpage, through a form containing open and closed fields, where the data may possibly not be record uniquely or regularly (KI).

- **Production and dissemination of information**

No mention was found of the amount and periodicity of publication of information from Notivisa-medicamento or from other data repositories belonging to the SINAF, as a form of feedback to the reporting sources and society^{41,53,58}.

The Anvisa website yielded four editions (two in 2012, one in 2013, and another in 2014) of a *Pharmacovigilance Bulletin* targeted to actors in the National Pharmacovigilance System aimed at "disseminating knowledge and orientation on the topic for health professionals, the Sentinel Network, and the state, municipal, and Federal District health surveillance agencies"⁵⁶. No space on the Anvisa website was dedicated to the publication of plans to minimize drug risks – a new pharmacovigilance strategy for risk-benefit assessment of new drugs and biologicals, in order to orient action by different sectors of society⁵⁹.

The pharmacovigilance area of Anvisa has published reports and safety alerts to disseminate information primarily to health professionals. From 2001 to 2015, 84 reports were published (average 5.6/year) that addressed drug safety issues⁶⁰. From 2000 to 2009, 67 alerts were published, of which 48 (72%) referred to ADRs⁶¹.

No publication addressed to common citizens was found that encouraged them to report ADEs or containing information on the possibility that any medication can increase health risks if not properly oriented and used correctly⁶⁰. In addition, the review did not yield any type of activity in detection, assessment, and monitoring of safety signals indicative of follow-up for medications suspected of causing adverse events.

Minimum requirements for a functional pharmacovigilance system

Box 2 summarizes part of the findings in the evolution of SINAF and its key elements, besides mentioning other information from the scoping review, e.g., the Anvisa Activities Report⁶², aimed at using the set of information to verify compliance with the minimum requirements proposed by the WHO.

Box 2

Description of the Brazilian National Pharmacovigilance System (SINAF) from January 1999 to March 2016, according to World Health Organization (WHO) minimum requirements.

Minimum requirements	Met/Unmet
1. National Pharmacovigilance Center	<ul style="list-style-type: none"> National Drug Monitoring Center (CNMM), hosted in Anvisa.
SINAF legal framework, structure, and functions	<ul style="list-style-type: none"> Federal provision: institutes the CNMM and defines its attributions. Spontaneous reporting is the traditional method; Legally mandatory reporting: DRM and health services. Reporting forms for DRM. Guidelines for risk management in pharmacovigilance for state, municipal, and Federal District health surveillance agencies. Periodic Safety Report: mandatory under federal law. Difficulties linking federal and state regulation of pharmacovigilance, e.g., much information from São Paulo State is not recorded in Notivisa-medicamento (KI). Surveillance network, featuring Sentinel. A national pharmacovigilance system to coordinate the surveillance needs to be defined in legal terms.
SINAF financing	<ul style="list-style-type: none"> No budget source was identified, earmarked for CNMM or the pharmacovigilance technical unit. In 2014, the total budget of Anvisa was BRL 792,499,510.00 * (BRL 3.96 per capita) to cover 130 organizational units, including divisions, departments, advisory bodies, etc. **.
SINAF staff	<ul style="list-style-type: none"> Anvisa had 2,125 employees in 2014 ⁶². In 2012, the pharmacovigilance technical unit had a staff of 12 ⁵⁶. The team's responsibilities include: assessment of causality between drug and adverse reaction, data analysis for signal detection, activities in communications, inspection in pharmacovigilance, and technical and administrative work (KI). No mention of the staff size working fulltime in the CNMM. Access to professional training in Brazil and abroad.
WHO Program for International Drug Monitoring	<ul style="list-style-type: none"> Brazil has been a member of the Program since 2001, collaborating with information on reporting of adverse drug reactions.
2. National spontaneous reporting system with form for adverse drug reactions	<ul style="list-style-type: none"> Notivisa-medicamento: main repository of spontaneous reporting data. Nationwide coverage. Uses standard online form for reporting suspected ADEs, especially adverse reactions, therapeutic ineffectiveness, and medication error. The form is too long. Drug poisoning has a specific form, integrated with Notivisa. Lay persons, patients, and family members report ADEs in a single form not integrated electronically with Notivisa. Many reports from the state of São Paulo reach Anvisa via electronic spreadsheets.
3. National database for recording and monitoring ADEs	<ul style="list-style-type: none"> Arrangement of the database prioritizes detection of safety signals by focusing on the drug-adverse event pair. This means that the presence of multiple pairs in the database may reflect the experience of only one patient. Mean annual reporting rate (2008 to 2013): 25 per million inhabitants ***.
4. Advisory committee on pharmacovigilance activities in the country	<ul style="list-style-type: none"> No exclusive advisory committee to support pharmacovigilance activities. CATEME focuses mainly on efficacy and safety issues in drug registration phase. Detection of post-marketing safety signals is relegated to lower priority.
5. Communications strategy for pharmacovigilance activities	<ul style="list-style-type: none"> The review identified risk communication strategies, mainly targeting health and health surveillance activities, such as bulletins, reports, and safety alerts and letters to health professionals. Effective direct communication with citizens is still a challenge. Innovative initiatives have encouraged reporting of ADEs in public health programs such as for TB and viral hepatitis.

ADEs: adverse drug events; Anvisa: Brazilian Health Regulatory Agency; CATEME: Technical Chamber on Medications; KI: key informant; Notivisa: National Reporting System for Health Surveillance; SINAF: Brazilian National Pharmacovigilance System.

Source: adapted from Maigetter et al. ¹.

* USD 299,056,418.90 (exchange rate: USD 1.00 = BRL 2.65);

** Brazil's population was 200 million in 2014;

*** The mean population during this period was 193,206,365 inhabitants.

Discussion

This study described and characterized the evolution and key elements of the SINAF, based on initiatives, especially by Anvisa, in addition to a comparative analysis of the minimum requirements for a functional pharmacovigilance system proposed by the WHO¹³. Although this was a descriptive study, the analysis represents a potential benefit for activities in the evaluation of SINAF and identification of its limitations¹, since questions related to its performance can be identified in this phase^{8,9}.

The characterization of pharmacogovernance further allows understanding a pharmacovigilance system like SINAF as a key structure not only for processing and analyzing ADEs, but also in the relations between the different stakeholders (users, health professionals, regulatory agents) in shaping the practices that lend a material basis to public drug safety policies. Although the CNMM meets the formal WHO requirements for a functional pharmacovigilance system, no documents and studies were identified that demonstrate its intentions and contributions to the consolidation of a national system, whether due to the characteristics of marked decentralization of actions in an inter-federative health system like the Brazilian one, or due to the absence of mechanisms for integration between the actions by CNMM and other activities in the country's pharmacogovernance structure.

The review also revealed some difficulties in clearly defining the organizational, functional, and budget structure of CNMM and GFARM and the key actors in the country's pharmacogovernance². No documents or studies were found that specified the budget allocations for programmatic pharmacovigilance activities in Brazil. Insufficient budgeting for pharmacovigilance activities has been described in some countries, like India, Uganda, and South Africa¹. As in other low and medium-income countries, the financing of GFARM/Anvisa activities is part of the overall budget for regulatory activities in Brazil, not specifically earmarked for pharmacovigilance¹² or to the CNMM. The literature also suggests a lack of equitable distribution of funds for monitoring and assessing drug safety in Brazil².

The creation of a technical area for pharmacovigilance at Anvisa and the definition of its attributions in 1999 were an undeniable step forward in the development of regulatory activities and in the shaping of SINAF itself. However, the scoping review found no legislation that formally instituted the SINAF, although discussions since 1995 point to the establishment of a national pharmacovigilance system⁶³. Documents produced by the technical area of Anvisa^{15,64}, scientific studies^{2,22,30,65}, and national policy legislation⁶⁶ have referred to this system, even questioning this formal gap³⁰ and justifying the need for its formal existence and functioning²⁵.

No studies were identified that evaluated strategies to encourage ADE reporting, although this is clearly a limiting factor for pharmacovigilance activities. Likewise, no documents were found that pointed to the need for prioritizing active reporting and recording methods for ADEs¹. Studies have shown that passive surveillance systems only capture 1% to 10% of adverse reactions⁶⁷, highlighting the importance of active surveillance methods in the identification of ADEs¹. The legal requirement of mandatory reporting by holders of drug registrations and health services can help reduce under-reporting in Brazil. In addition, the Reporting by Pharmacies and Sentinel Physicians programs have the potential to expand ADE reporting and recording, although their participation thus far has been virtually nonexistent^{2,46}.

Although the staff size for pharmacovigilance activities at the federal level meets the minimum requirements from WHO (at least in terms of fulltime staff), the needs are broader for monitoring adverse events in a decentralized health system and in a country with continental dimensions like Brazil. Staff shortage was identified as an important challenge in pharmacovigilance systems in low and medium-income countries¹² like India, Uganda, and South Africa¹, among others.

During the period analyzed here, no legal instrument was identified that established an advisory committee in pharmacovigilance to provide technical consultation to SINAF, particularly in terms of the activities developed by the CNMM, thus compromising full compliance with the minimum requirements for a functional pharmacovigilance system proposed by WHO¹³. However, on November 7, 2017, under *Ruling n. 1,857*⁶⁸, Anvisa established a Technical Chamber on Pharmacovigilance to respond to the need for this committee. Since this committee only began to function more recently, it was not possible to conduct a more in-depth analysis of its influence on SINAF.

The ADE reporting rate in Brazil in 2011 (29/million inhabitants) was substantially lower than that in South Africa (77/million), higher than in India (15/million) ¹ and far short of the target proposed in the international literature, suggesting 300 reports per million inhabitants ⁶⁹. Some reasons for the low reporting rate include health professionals' perception that the task of reporting ADEs means even more work in an already busy schedule, besides reporting of other health problems, lack of specific training for physicians and pharmacists, and rare government initiatives to encourage reporting of ADRs ¹. The effective implementation of strategies like Sentinel Physicians and Reporting by Pharmacies and emphasis on training of health professionals at the graduate level may contribute to increasing ADE reporting rates in Brazil. The low reporting rates, plus reporting by patient/families/common citizens and the state of São Paulo outside the Notivisa-medicamento system hinder the detection and monitoring of safety signals, risk assessment, and adoption of the necessary regulatory measures to protect patients ¹.

The scoping review indicates inequalities in the current forms of risk reporting by identifying drug safety problems ². GFARM publishes various documents targeted mainly to health professionals. However, effective communication targeted to laypeople is still a challenge. In order for any pharmacovigilance system to be effective, it needs to define communication strategies with laypeople/patients and health professionals and between these two groups and society ⁷⁰. Failure to publicize drug risk mitigation plans was another gap identified by the review. Health professionals should be familiar with the main information contained in these documents in order to better guide their clinical practice and thus minimize patients' health risks ⁵⁹.

The study's limitations can be attributed to the characteristics of a scoping review, including the process of identification, selection, and analysis of the publications and the document analysis conducted from the authors' perspective, whether as a function of their understanding of pharmacovigilance activities or because document analysis may not suffice to identify all the elements in pharmacovigilance policies. Scoping reviews usually pose research questions that are broader than in systematic reviews, in addition to the more qualitative methods in summarizing the results, aimed at identifying parameters and gaps in specific themes ⁷¹.

Some other sources of international data were not included, such as Embase, International Pharmaceutical Abstracts (IPA), Web of Science, and Scopus, so that some relevant studies may not have been identified. A study on the scientific research on health surveillance of medications in Brazil, and which searched the above-mentioned databases, found 16 studies related to "pharmacovigilance" from 1999 and 2011 ⁷². Of these, only five studies were aligned with our research question, and all of them had been identified in phase 1 of the scoping review, which aims to explore patterns and thus is not intended to produce an exhaustive literature search ⁷³.

The authors' personal perception may have influenced the identification and selection of publications in Google, the Brazilian National Press, and especially in the Anvisa website, considering the inherent limitations in the latter's search system. The search in Google may have missed some publications, due to the predefined cutoff after the first 100 results. In addition, no specialist was contacted to suggest additional relevant publications that may not have been included in the scoping review. The difficulties in retrieving the gray literature may also have influenced the results. Another limitation relates to the review's objective, i.e. to describe and characterize the SINAF from the perspective of activities developed by Anvisa, without focusing on the state, municipal, and Federal District health surveillance agencies and other relevant actors in Brazil's pharmacogovernance. The study's findings may thus reflect only part of the SINAF.

Although this review had not originally planned to assess the publications' methodological quality, particularly that of the scientific studies, two studies were excluded from the full text analysis stage, since they presented important quality problems, based on the researchers' experience. The need to assess the studies' quality should address the challenges with assessment of the types and amount of publications and the study models that can be included in the review, which may or may not exclude the study itself ⁷⁴. In our review, most of the publications were technical and legal document that proved at least as important as the scientific articles and were essentially sufficient to help characterize the SINAF.

Drug safety and effectiveness require regulatory and pharmacogovernance systems ² and particularly a functional pharmacovigilance system, since the safety profile of many drugs studied in

developed countries may not necessarily be generalizable to developing countries, where the incidence, usage pattern, individual risk behaviors, and severity of adverse reactions may differ considerably because of the environment and genetic factors⁷⁵. However, there are real concerns that impact the capacity of SINAF to monitor and effectively control the pharmaceuticals market in Brazil, one of the world's largest and with a growing demand⁷⁶. For example, the mean reporting rate per million inhabitants according to this study suggests lack of sufficient size to significantly detect safety signals. Given the key role of pharmacovigilance systems in establishing pharmacogovernance practices and infrastructure in the country, the analysis of the characteristics and limitations of the SINAF represents a potential contribution to both the improvement of the system itself and strengthening of public drug safety policies in Brazil.

Contributors

D. M. Mota, A. Vigo, and R. S. Kuchenbecker participated in the study conception and design and the article's data analysis and interpretation. D. M. Mota wrote the article, and A. Vigo and R. S. Kuchenbecker participated in the critical revision and final approval.

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Resumo

Esta revisão de escopo objetiva descrever e caracterizar o sistema de farmacovigilância do Brasil (SINAF) e averiguar o atendimento aos requisitos mínimos propostos pela Organização Mundial da Saúde para um desempenho funcional de sistemas nacionais dessa natureza. A estratégia de pesquisa bibliográfica utilizou recomendações do STARLITE e termos de busca nas bases de dados MEDLINE/PubMed, Google, Imprensa Nacional e website da Agência Nacional de Vigilância Sanitária (Anvisa), compreendendo o período entre 1999, ano de criação da Anvisa, e março de 2016. Foram incluídas 47 (4,4%) publicações, de um total de 1.068 identificadas, prevalecendo, nesta ordem: 14 normas jurídicas (29,8%), 13 (27,6%) documentos técnicos e 10 (21,3%) artigos científicos. Os estudos e documentos técnicos analisados compreenderam a criação, em âmbito federal, da primeira unidade técnica de farmacovigilância, o sistema de notificação de eventos adversos, o Centro Nacional de Monitorização e a Câmara Técnica de Medicamentos. A taxa de notificação de eventos adversos a medicamentos no Brasil correspondeu, em 2013, a 36 notificações/1 milhão de habitantes, bastante inferior à meta proposta na literatura internacional, que sugere 300 notificações/1 milhão de habitantes. Este estudo identificou aspectos estruturais e funcionais que podem comprometer o desempenho do SINAF, como a falta de legislação que institua oficialmente o próprio sistema e suas finalidades.

Avaliação em Saúde; Sistemas de Informação em Saúde; Farmacovigilância; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Sistemas de Notificação de Reações Adversas a Medicamentos

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Evaluación en Salud; Sistemas de Información en Salud; Farmacovigilancia; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Sistemas de Registro de Reacción Adversa a Medicamentos

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Approved on 25/Jul/2018

Mota DM, Vigo A, Kuchenbecker RS. Evolution and key elements of the Brazilian pharmacovigilance system: a scoping review beginning with the creation of the Brazilian Health Regulatory Agency. Cad Saúde Pública 2018; 34(10):e00000218.

doi: 10.1590/0102-311XER000218

The journal has been informed about some errors in the paper. The corrections are follows:

Where it reads:

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