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Brazil Case Study

Pharmacovigilance in Brazil

Creating an Effective System in a Diverse Country

Huihui Wang
Albert Figueras
Patricio V. Marquez
Kseniya Bieliaieva

With contribution from Luana Araujo

Korea-World Bank Partnership Trust Fund (KWPF)

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1818 H Street NW
Washington DC 20433
Telephone: 202-473-1000
Internet: www.worldbank.org

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Acronyms

ADE	Adverse drug event
AEFI	Adverse effect following immunization
ANVISA	*Agência Nacional de Vigilância Sanitária*
CNMM	*Centro Nacional de Monitorização de Medicamento*s
CVS-SP	*Centro de Vigilância Sanitária* (São Paulo)
GFARM	*Gerência de Farmacovigilância*
GPUIM	Group for the Prevention of Improper Use of Pharmaceuticals
ICH	Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
NOTIVISA	*Sistema Nacional de Notificações para a Vigilância Sanitária*
PERI	*Programa Estadual de controle de Iatrogenias*
PMID	Program for International Drug Monitoring (WHO)
PV	Pharmacovigilance
Sinitox	*Sistema Nacional de Informações Tóxico – Farmacológicas*
SNVS	*Sistema Nacional de Vigilância Sanitária*
VIGIPOS	*Sistema de Notificação e Investigação em Vigilância Sanitária*
WHO	World Health Organization

Overview

Starting and developing an effective pharmacovigilance (PV) system based on reporting adverse effects of medicines and vaccines is a well-recognized way to improve patients safety. Notwithstanding this, the size and complexity of Brazil has presented particular challenges in developing and consolidating an effective pharmacovigilance (PV) system, with lessons and experiences that may be of particular interest. It has 212 million inhabitants,[1] ranking as the sixth most populated country and its population is very diverse. Geographically, it is the largest country in Latin America and fifth in the world, after Russia, Canada, the United States, and China. Furthermore, Brazil is a federative republic organized in 26 states and is classified as an upper-middle-income country.

According to the 1988 Federal Constitution and several Laws (Leis 8.080/90 and 8.142/90), Brazilian healthcare management and policies depend on a decentralized but integrated system involving the central government, the states and the municipalities. In practice, this means that the responsibilities of the healthcare sector are distributed between the three government levels.

In August 2001, Brazil became the 62nd country admitted to the World Health Organization Program for International Drug Monitoring (PMID). But, as in many other countries, pioneering work to monitor the safety of medical treatments actually started long before. Once the Brazilian Health Surveillance Agency (Portuguese: *Agência Nacional de Vigilância Sanitária*, ANVISA) was created and deployed, PV in Brazil became a harmonized program covering all 26 states, using a common reporting form and, since 2018, a common database (VigiMed).

As of February 2022, VigiMed contained more than 98,000 reports of suspected adverse drug reactions collected since 2018. The leading state in reporting volume is São Paulo (accounting for 20 percent of all Brazilian reports).[2]

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[1] World Bank, "Brazil Country Report," from online database, available at https://databank.worldbank.org/views/reports/reportwidget.aspx?Report_Name=CountryProfile&Id=b450fd57&tbar=y&dd=y&inf=n&zm=n&country=BRA.

[2] ANVISA, "Notificações de farmacovigilância," webpage, https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas/notificacoes-de-farmacovigilancia.

Pharmacovigilance plays a vital role in ensuring that patients receive appropriate vaccines and medicines that are safe and effective.

1. Introduction

The ability to oversee and monitor the use of all newly authorized drugs and vaccines, both brand-name and generic, is critical to ensure that they work correctly and that their health benefits outweigh their known risks when used in daily clinical practice. This process, known as pharmacovigilance, plays a vital role in ensuring that patients receive appropriate vaccines and medicines that are safe and effective.

While this may seem obvious, the process of building the necessary capacity and even recognition of the importance of this work has taken decades. A key starting point occurred in 1968, with the creation of the World Health Organization (WHO) Program for International Drug Monitoring (PIDM). Since then, attention to these issues including surveillance of adverse drug effects (ADEs) caused by new vaccines and medicines gradually spread and has now become a matter of global interest.

Brazil is a particularly notable example because it ranks in the top five amongst the largest and the most populated countries—two characteristics that difficult the deployment and consolidation of a pharmacovigilance system. **This report reviews this experience.**

2. The Beginning: Initial Steps in Pharmacovigilance in Brazil

In Brazil, the passage of Law 6360 (Sept. 23, 1976) was an important milestone: establishing that medications, drugs, pharmaceutical supplies, healthcare products, cosmetics, and sanitizers are subject to health surveillance.[3]

Turning the law into actual surveillance was the next step. In that regard, an important advance was the establishment in 1980 of the National System for Toxico-Pharmacological Information (Portuguese: *Sistema Nacional de Informações Tóxico – Farmacológicas* (Sinitox)), a pioneering surveillance activity that created a continuous flow of information concerning the available medicines. Although Sinitox was not formally considered a pharmacovigilance (PV) system, it did collect information on cases of intoxication and poisoning from 31 regional centers, with a total of 386,861 cases reported as of 1995.[4] Among these cases of intoxication, there were a few ADEs—a reporting area that lies at the heart of effective PV work.[5]

Similarly to other countries, the first PV-specific activities in Brazil started in universities, drug information centers, and health professionals' associations during the 1990s. For example, in the northeast state of Ceará, the Group for the Prevention of Improper Use of Pharmaceuticals (Portuguese: *Grupo para a Prevenção do Uso Inapropriado de Medicamentos)* GPUIM), based in hospital pharmacies, served as drug information centers and conducted pharmacovigilance activities.[6] GPUIM started its activities in 1990, but it was officially recognized by the end of 1995. One of its first research projects that had an international impact involved the detection of off-label, over-the-counter use of misoprostol (a medicine prescribed for gastric disorders) for abortion.[7] In 1990, abortion was illegal in Brazil and "day after" pills were not yet marketed. As a result, misoprostol started to be used for its abortifacient effect. However, to be effective, misoprostol should be used appropriately and under careful healthcare supervision, which was not the case when it was being used for abortions. This led to continued pregnancies and exposure of the fetuses to a medicine which causes severe congenital malformations. Publications of this problem appeared in *The Lancet*, and were used as a reference by the U.S. Food and Drug Administration in deciding to include a warning on the label of that product.[8]

Additionally, in 1997, consumer advocacy groups and pharmacy societies led by SOBRAVIME (the Brazilian Society for Medicines Surveillance; Portuguese: *Sociedade Brasileira de Vigilância de Medicamentos*) organized the SOBRAVIME IV International Congress focusing on PV in the southern state of Paraná. This event helped to bring together Brazilian health professionals interested in PV and share discussions with experts working in the field in other countries.

So, during this period, ideas from participants in the global pharmacovigilance movement sparked discussions in Brazil concerning nationwide systems; and the ideas from the global level complemented the national pharmacovigilance initiatives and regulations in Brazil.[9,10]

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[3] Law no. 6,360 of September 23, 1976, DISPÕE SOBRE A VIGILÂNCIA SANITÁRIA A QUE FICAM SUJEITOS OS MEDICAMENTOS, AS DROGAS, OS INSUMOS FARMACÊUTICOS E CORRELATOS, COSMÉTICOS, SANEANTES E OUTROS PRODUTOS, E DÁ OUTRAS PROVIDÊNCIAS, (English translation) https://www.emergobyul.cn/sites/default/files/file/lei_6.360_1976_health_surveillance_standards.pdf.

[4] S. Rozenfeld, "Farmacovigilância: elementos para a discussão e perspectivas," *Cadernos de Saúde Pública* (April 1998) 14(2):237–63, https://doi.org/10.1590/S0102-311X1998000200002.

[5] The "term adverse drug event" (ADE) refers to any medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment.

[6] H.L. Coêlho, P.S. Dourado Arrais, and A. Parente Gomes, "Sistema de Farmacovigilância do Ceará: um ano de experiencia," *Cadernos de Saúde Pública* (September, 1999) 15(3):631–40, https://doi.org/10.1590/S0102-311X1999000300021.

[7] H.I. Coelho, C. Misago, W.V. da Fonseca, D.S. Sousa, and J.M. de Araujo. "Selling Abortifacients Over the Counter in Pharmacies in Fortaleza, Brazil," *The Lancet* (1991) 338(8761):247, https://doi.org/10.1016/0140-6736(91)90379-4,.

[8] HL Coelho, "Misoprostol – A solucão não é tao simples," *Rev. Saúde Pública (1998) 32(4),* https://doi.org/10.1590/S0034-89101998000400013.

[9] K.G. Palma Rigo and P. Nichiyama, "A evolução da farmacovigilância no Brasil," *Acta Scientiarum. Health Sciences* (2005) 27(2):131–35, http://www.redalyc.org/pdf/3072/307223952005.pdf.

[10] K. Moscou, J.C. Kohler, and A. MaGahan, "Governance and Pharmacovigilance in Brazil: A Scoping Review," *Journal of Pharmacological Policy and Practice* (2016) 9(3), https://doi.org/10.1186/s40545-016-0053-y.

3. Pharmacovigilance in São Paulo

São Paulo is the wealthiest state in Brazil (it accounts for 30 percent of Brazil's gross domestic product), and it earned the nickname "locomotive of Brazil." The capital city of the same name, with a population of over 12 million, is the most populous city in the Americas and the fourth largest globally. This prosperous and industrialized state has many renowned universities, research centers, and tertiary-level public and private hospitals. It should also be noted that the Brazilian medicines market (US$17.04 billion in 2017, US$21 billion in 2020) ranked 10th among the top national pharmaceutical markets worldwide; and within Brazil, São Paulo is the center of the pharmaceutical industry. With more than half of the national and international companies operating in the country based in the state, it is not surprising that São Paulo was among the first states in Brazil to start PV activities.

Efforts in the state began in the 1990s, and in 1998, the Health Surveillance Centre in São Paulo (Portuguese: *Centro de Vigilância Sanitária*, CVS-SP) established a set of programs to:

- Set up the inspection of pharmaceutical industries to ensure the production quality;
- Build up an information system related to the registry of medicines and the listing of existing manufacturers;
- Establish health inspections at different levels; and
- Promote the rational use of medicines.

The São Paulo authorities also established the state program for the iatrogenic control (Portuguese: *Programa Estadual de controle de Iatrogenias,* PERI)[11] to: (1) promote epidemiological research on ADEs; (2) operationalize the flow of reports; and (3) facilitate training staff to conduct these activities.

In parallel, a commission made up of members from relevant state universities and hospitals provided counsel and guidance to the CVS-SP. The initial PV team consisted of a couple of medical and pharmaceutical professionals, interns, and one national and one international medical consultant. This team started working with the routine analysis of the reports they were receiving, mostly from manufacturers, public and private hospitals, and a few health professionals working in primary health care.

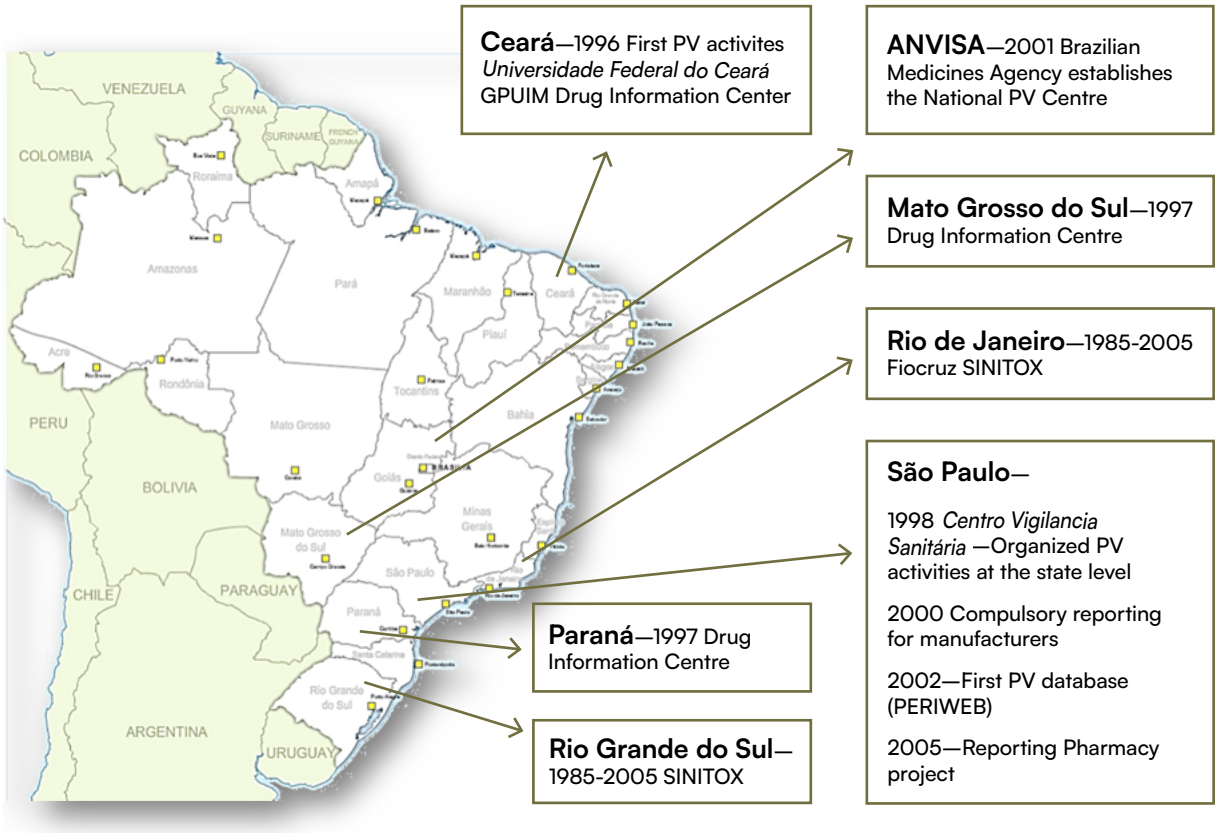
To increase reporting by health professionals, the CVS-SP conducted many dissemination activities in different fora (e.g., articles in journals published by the local medical council and attending national medical and pharmaceutical meetings in São Paulo). In addition, the CVS-SP published a bulletin called *Alertas terapêuticos* (*Therapeutic Alerts*) to share information on newly reported severe or previously unknown ADEs, mostly associated with recently marketed medicines.

A major advance was the enactment of a new regulation (Portaria CVS no. 10, de 22/11/2000) in 2000, which made ADE reporting compulsory for all manufacturers with headquarters in São Paulo state. This initiative, which reflected common practice for international manufacturers, was designed to increase the engagement of local manufacturers in the safety of medicines. Nine years later, a federal law extended this measure to the entire country.

From its inception until its replacement in 2018 by the ANVISA database described later in this chapter, the PV program in São Paulo continued growing and strengthening, with a specific database (PERIWEB) including all the received reports information. A few previously unknown ADEs were described, and the traditional PV activities based on spontaneous reporting were complemented by some specific active PV programs, especially in selected hospitals. For example, the CVS-SP created a network involving 11 hospitals which regularly reported to the PERIWEB. During a search for potential signals, 33 cases of chemical conjunctivitis in newborn babies were found. (In certain countries, instilling eye drops of silver nitrate just after delivery was a common practice to prevent eye infections.) That cluster of cases led to different activities to identify additional cases and to try to strengthen that association. One year later, six hospitals had identified and reported 622 cases. Despite being an already

[11] "Iatrogenic" is any condition, illness, or symptoms induced as the result of a physician's actions or the healthcare environment. Usually, we call "iatrogenic" any consequence of taking a medicine prescribed by the physician.

Figure 1 Pharmacovigilance Activities in Different Brazilian States before National Consolidation within the Brazilian Medicines Agency (ANVISA)



Source: For the map itself: map.comsersis.com (https://map.comersis.com/carte-Vector-map-of-Brazil-states--cm03t21c436.html),and source for the annotations: author's work.
Note: GPUIM = Group for the Prevention of Improper Use of Pharmaceuticals (Portuguese: *Grupo para a Prevenção do Uso Inapropriado de Medicamentos*); SINITOX = National System of Toxico-Pharmacological Information (Portuguese: *Sistema Nacional de Informações Tóxico – Farmacológicas*).

known and mild adverse effect of these eye drops, the reaction scared the new parents. In response, the PV team led group discussions with the hospitals and povidone-iodine was recommended as a substitute for silver nitrate.[12]

Notwithstanding this, although some Brazilian states such as São Paulo started to consolidate a functional PV program which obtained some results, most Brazilian states did not follow that course. The problem was that each state moved at its own pace, determined by the available resources and trained health professionals. Additionally, there was no common PV database. Figure 1 highlights some of the PV activities conducted before 2005. As a result of these factors, harmonization of these state-based efforts became necessary.

[12] B.M. Napchan, R.P. Morales, M.L. Carvalho, K.V. Cunha, and A. Figueras, "From Suspicion to Action: The Chemical Conjunctivitis and Silver Nitrate Connexion Example in Brazilian Hospitals," *Pharmacoepidemiology and Drug Safe*ty (2005) 14: 555–59, https://doi.org/10.1002/pds.1050.

4. The creation and consolidation of ANVISA

ANVISA's establishment and coordinating bodies.

In 1990, the Federal Law (Lei 8080/90, Sept. 19, 1990) made provisions for creating commissions and defining policies and programs for the surveillance of medicines.[13] It took sometime, however, before a federal agency was established to carry out this function in the health system nationwide. The Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA) was established by Law 9782, of January 26, 1999.[14]

ANVISA is a self-governed body linked to the Ministry of Health, with administrative independence, stability of its directors and financial autonomy. It is part of the Unified Health System (SUS) as the coordinator of the National Health Surveillance System (SNVS), and is active throughout the Brazilian territory (see https://www.gov.br/anvisa/pt-br).[15]

Its structure is complex (Figure 2); the different managing units (*Gerências*) belong to any of the five Directorates (*Diretorias*). Pharmacovigilance activities are part of the *5th Diretoria*.

ANVISA's mandate.

ANVISA is responsible for regulating and approving pharmaceutical products, establishing and enforcing sanitary standards, and regulating the food industry. It is also responsible for: (i) coordination of the National Health Surveillance System (*Sistema Nacional de Vigilância Sanitária*, SNVS), the National Program of Blood and Blood Products, and the National Program of Prevention and Control of Hospital Infections; (ii) monitoring the prices of medicines and medical devices; (iii) overseeing the regulation, control, and inspection of smoking products; and (iv) providing relevant technical support for the granting of patents by the National Institute of Industrial Property.

In the area of sanitary control, ANVISA is responsible for protecting the population's health by exercising sanitary control over the production and marketing of products and services subject to sanitary surveillance. This includes premises and manufacturing processes and the full range of relevant inputs and technologies. In addition, ANVISA exercises control over ports, airports, and borders, and also liaises with the Brazilian Ministry of Foreign Affairs and foreign institutions on international aspects of sanitary surveillance.

Overall, ANVISA regulates medicinal products for human use, medical devices, food, cosmetics, and sanitizers. The total number of staff at ANVISA is approximately 1,600, including 200 reviewers of marketing authorization/product licenses, who are primarily pharmacists. The total annual budget of about US$840 million is 40 percent government funded and 60 percent fee based.[16]

ANVISA's 5th *Diretoria* formulates guidance to establish strategies to monitor the quality and safety of products and services related to health surveillance. This includes:

- Monitoring the population's health at ports, airports, and borders
- Monitoring activities concerning the import and export of products related to health surveillance
- Pharmacovigilance
- Risk management of products related to health surveillance

Essentially, ANVISA's 5th *Diretoria* is responsible for surveillance to ensure that premarketing safety conditions are maintained during the post marketing stages. These activities constitute the analytic intelligence of the national system of health monitoring. The monitored products include medicines, vaccines,

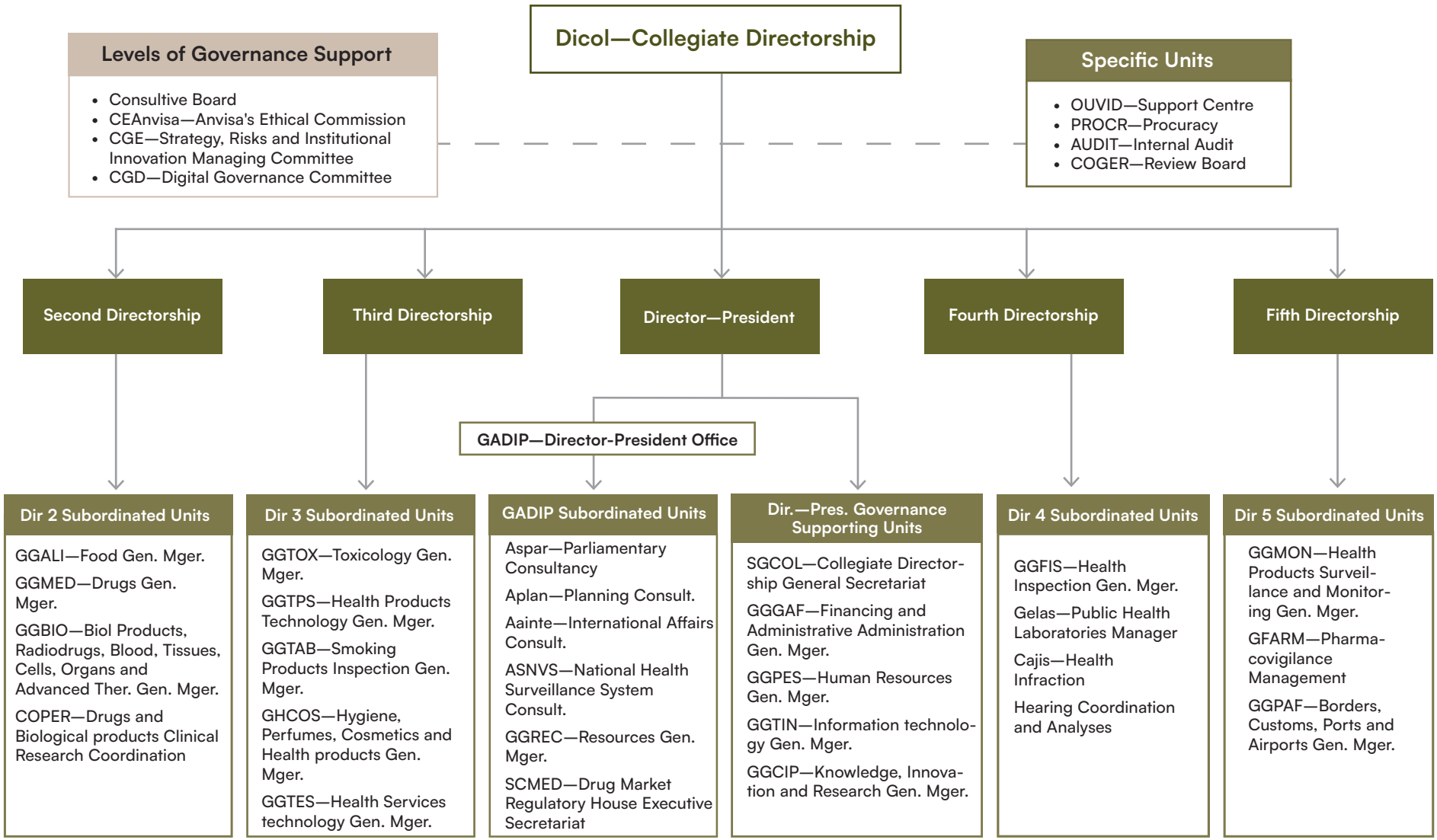
[13] Lei Federal no. 8080/90 (Sept. 19, 1990), https://www.saude.mg.gov.br/index.php?option=com_gmg&controller=document&id=7576.

[14] Lei no. 9782 (Jan. 26, 1999). https://www.planalto.gov.br/ccivil_03/leis/l9782.htm

[15] Moscou et al., "Governance and Pharmacovigilance in Brazil: A Scoping Review."

[16] Patel P, Cerqueira DM, Santos GML, de Lima Soares R, Sousa VD, Liberti L, McAuslane N. 2020. "A Baseline Analysis of Regulatory Review Timelines for ANVISA: 2013-2016". Ther Innov Regul Sci. 54(6):1428-1435. doi: 10.1007/s43441-020-00169-5. Epub 2020 Jun 9. PMID: 32519282; PMCID: PMC7704494.

Figure 2 ANVISA Organigram



Source: ANVISA, https://www.gov.br/anvisa/pt-br/acessoainformacao/institucional/arquivos/organograma.pdf/view.

food, hygienic products, cosmetics and perfumes, blood, cells, and human tissues and organs.[17]

The *Gerência de Farmacovigilância* (Pharmacovigilance Managing Body, GFARM) belongs to the 5*th Diretoria* and was established just after the creation of ANVISA. Following this, the National Center for Medicines Monitoring (*Centro Nacional de Monitorização de Medicamento*s, CNMM), hosted by GFARM, was created in 2001 after Directive 696 (May 2001) to strengthen PV actions and contribute to the rational use of medicines. It was established in 2001, months before Brazil joined the WHO-PMID (see Table 1).

[17] ANVISA, "Atribuições," available at https://www.gov.br/anvisa/pt-br/composicao/quinta-diretoria/atribuicoes.

Table 1 Key Laws and Regulations Related to Pharmacovigilance in the National Pharmacovigilance System in Brazil (1976—2021)

Law/Regulation	Topic / Key sentence
Law no. 6.360 (Sept. 23, 1976)	Article 79 "...all the reports about accidents or noxious reactions produced by medicines will be sent to the health authority..."
Directive no. 577 (Dec. 20, 1978)	Recommended that the *Câmara Técnica de Medicamentos* (Medicines Technical Board) of the *Conselho Nacional de Saúde* (National health Council) "...adopt necessary measures to implement a national system of pharmacological surveillance, with the aim of reporting, registering and assessment of the adverse reactions to the medicines registered by the Ministry of Health..."
Directive MS/SVS no. 40 (May 9, 1995)	Introducing a commission to propose the National System of Pharmacoepidemiology.
Directive no. 3.916 (Oct. 30, 1998)	Approving a National Medicines Policy that had two directives: (i) the sanitary regulation of medicines; and (ii) the guarantee of the safety, efficacy, and quality of medicines.
Directive no. 6 (Jan. 29, 1999)	Article 89: "...the local Health Authority must establish mechanisms to conduct the pharmacovigilance of medicines based on the substances listed in Portaria SVS/MS no. 344/98 and its updates when they are considered of increased risk for individual and collective health..."
Law no. 9.782 (Jan. 26, 1999)	Creating the *Agência Nacional de Vigilância Sanitária* (Brazilian Health Surveillance Agency, ANVISA) to establish, coordinate, and monitor the toxicological and pharmacological vigilance systems.
Directive MS no. 696 (May 7, 2001)	Creating the *Centro Nacional de Monitorização de Medicamentos* (Brazilian Medicines Monitoring Centre, CNMM), located in ANVISA's *Unidade de Farmacovigilância* (Pharmacovigilance Unit).
Resolution RDC no. 136 (May 29, 2003)	Requiring that the marketing authorization holders present pharmacovigilance data according to the structure of the Periodic Safety Update Report/International Conference on Harmonization to renew medicines' registries by ANVISA.
Directive ANVISA no. 354 (Aug. 11, 2006)	Approving and promulgating ANVISA's internal rules.
Resolution RDC no. 04 (Feb. 19, 2009)	Establishing the pharmacovigilance rules for marketing authorization holders.
Directive n° 1.660 (July 22, 2009)	Putting in place the *Sistema de Notificação e Investigação em Vigilância Sanitária* (Health Monitoring System for Reporting and Research, Vigipós) in ANVISA.

Table 1 (CONT) Key Laws and Regulations Related to Pharmacovigilance in the National Pharmacovigilance System in Brazil (1976—2021)

Law/Regulation	Topic / Key sentence
Regulatory Instruction IN no. 14 Oct. 27, 2009)	Approving pharmacovigilance guidance.
Resolution RDC no. 55 (Dec.16, 2010)	Setting out the registry of new biological products.
Resolution RDC no. 36 (July 25, 2013)	Instituting compulsory reporting of adverse events by the Patient Safety Nucleus of each Health Service.
Resolution RDC no. 51 (Sept. 29, 2014)	Setting the *Rede Sentinela* (Sentinel Network) for the National System of Health Surveillance which was created in 2002
Directive no. 1.856 (Nov. 7, 2017)	Establishing the *Câmara Técnica de Farmacovigilância* (Pharmacovigilance Technical Board)
Resolution RDC no. 200 (Dec. 26, 2017)	Updating the registry and renovation of new medicines authorization
Resolution RDC no. 406 (July 22, 2020)	Enumerating the Good Pharmacovigilance Practices for Marketing Authorization Holders for human use
Regulatory Instructions IN no. 63 (July 29, 2020)	Setting out the Periodic Benefit-Risk Evaluation Report (PBRER) to be submitted to ANVISA by marketing authorization holders
Resolution RDC No. 585 (Dec. 10, 2021)	Approving and promulgating ANVISA's updated internal rules.

Sources: V.L.E. Pepe and H.M.D. Novaes, "National Pharmacovigilance Systems in Brazil and Portugal: Similarities, Differences, and Challenges," *Cad. Saúde Pública* (2020) 36 (7), https://doi.org/10.1590/0102-311X00043019; and ANVISA, RDC no. 406/2020 e IN no. 63/2020, https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/farmacovigilancia/rdc-no-406-2020-e-in-no-63-2020.

CNMM is located in ANVISA, and represents Brazil in the WHO PIDM. Its activities include: collecting and evaluating reports; developing the database and periodic analyses to assess the rational and safe use of medicines; disseminating information to health professionals and the general population; proposing regulatory measures to protect the health of medicines' users; and sending reports to the WHO -PIDM.[18]

Monitoring ADEs is a key component of ANVISA's work at the national level. To facilitate ADE reporting, ANVISA provided all health professionals with access to the *Sistema Nacional de Notificações para a Vigilância Sanitária* (National System for Health Monitoring Reporting, NOTIVISA), a national, web-based computerized reporting system started in 2006 to receive, register, and process reports of suspected and confirmed cases of ADEs and technical complaints. ADE reports include suspected adverse drug reactions, cases of therapeutic inefficacy, and medication errors causing ADEs. It is important to highlight that this includes interactions between medicines causing unwanted outcomes, problems associated with the off-label use, and abuse of medicines. Technical complaints comprise suspected alterations or irregularities associated with products and manufacturers.

The ANVISA ADE reporting process also uses additional guidance. As a full member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), ANVISA adopted the Medical Dictionary for Regulatory Activities (MedDRA), a comprehensive terminology developed by ICH to standardize medical

[18] *Associação Brasileira das Empresas do Setor Fitoterápico, Suplemento Alimentar e de Promoção da Saúde* (ABIFISA), "Centro de Monitorização de Medicamentos completa 20 anos," news release (July 5, 2021), available at https://abifisa.org.br/centro-de-monitorizacao-de-medicamentos-completa-20-anos/.

terms including medicines and ADEs in several languages, including Portuguese.[19]

In 2009, the law RDC no. 04/09 detailed the PV regulations specifically addressed to all manufacturers with a medicinal product authorized in the country for human use.[20] The law also states that all pharmaceutical companies operating in Brazil must have a PV department and details certain requirements concerning the composition of those departments and their reporting obligations. Previous laws already regulated different aspects of PV. However, prior to the 2009 law, reporting by manufacturers was not compulsory at the national level; it was mandatory only in a few states such as São Paulo.

Also in 2009, the Health Monitoring System for Report and Research (*Sistema de Notificação e Investigação em Vigilância Sanitária*, VIGIPOS) was established to strengthen post-marketing surveillance of medical products. Operating within the framework of the SNVS as a part of the unified health system (*Sistema Único de Saúde,* SUS), VIGIPOS was specifically mandated to monitor, analyze, and research ADEs and technical complaints related to services or products under the sanitary surveillance umbrella.[21] VIGIPOS activities are designed to (1) measure the impact of the use of products as well as services adopting or not good practices; and (2) recommend preventive and corrective measures to avoid adverse events caused by not following the established processes. To share relevant information, VIGIPOS generates alerts addressed to hospitals, institutions, clinical wards, and health professionals describing these events.

To assess the performance of the medication module of NOTIVISA, a health evaluation study was conducted between 2008 and 2013 using eight attributes established by international guidelines to assess public health surveillance systems: simplicity, acceptability, representativeness, completeness, and validity, consistency, and positive predictive error and timeliness.[22] During the study period, 63,512 reports were identified in the database; most of them were severe (60.5 percent). The performance of NOTIVISA was considered satisfactory regarding two of the eight attributes (validity and positive predictive error) and deficient in the six remaining attributes (simplicity, acceptability, representativeness, completeness, consistency, and timeliness). As a result of these findings, the authors concluded that the system needed to be improved.

[19] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *Understanding MedDRA: The Medical Dictionary for Regulatory Activities* (2013), https://admin.meddra.org/sites/default/files/main_page_slideshow/meddra2013_0.pdf.

[20] Resolution RDC no. 04 (Feb. 10, 2009), https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2009/res0004_10_02_2009.html.

[21] *Centro de Vigilância Sanitária, PORTARIA MS* Nº 1.660, DE 22 DE *JULHO DE* 2009, https://cvs.saude.sp.gov.br/zip/U_PT-MS-1660_220709.pdf.

[22] D.M. Mota, Á. Vigo, R.S. Kuchenbecker, "Avaliação do desempenho do Sistema Nacional de Notificações para a Vigilância Sanitária: uma ferramenta do sistema de farmacovigilância no Brasil" [Evaluation of the Performance of the Brazilian Notification System for Health Surveillance: A Tool in Brazil's Pharmacovigilance System], *Cien Saúde Coletiva* (2020) 25(5):1955–66, https://doi.org/10.1590/1413-81232020255.19522018.

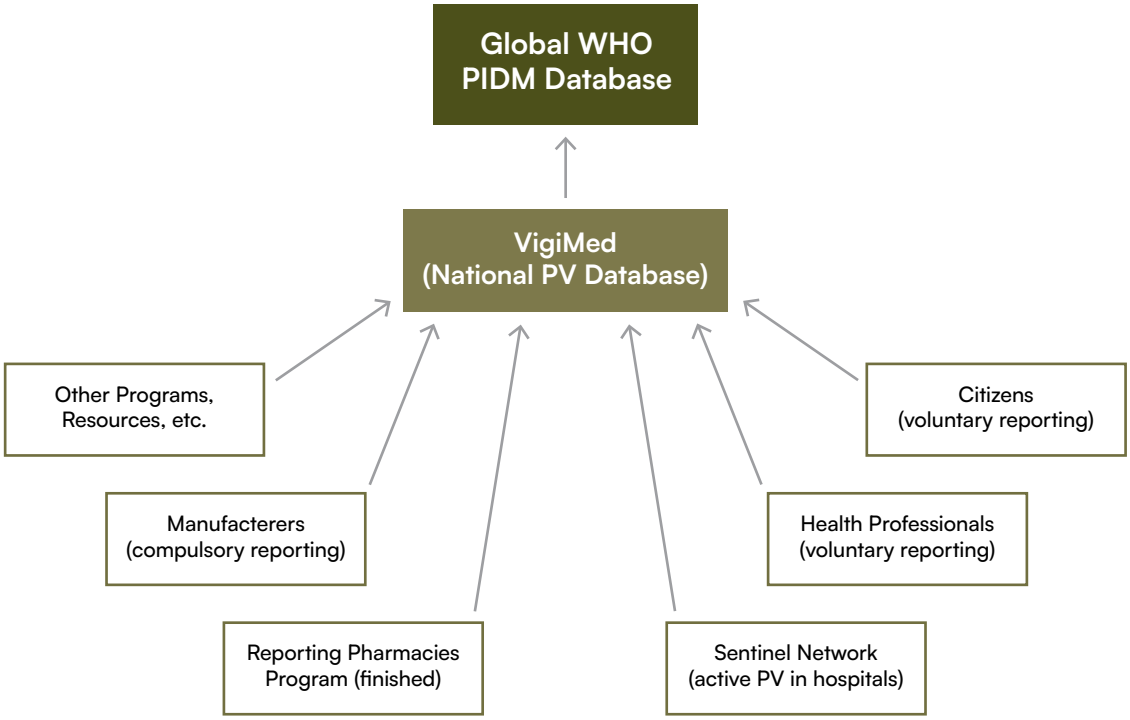
A new standardized database

In 2018, GFARM, jointly with the Uppsala Monitoring Centre (UMC, and coordinator of the WHO PIDM network), replaced NOTIVISA with a new reporting system known as VigiMed (Figure 3). While it is based on the WHO PIDM database VigiFlow, VigiMed is tailored specifically for Brazil. This approach allows VigiMed to ensure the harmonization of the national PV program with international standards. It also benefits from different outputs, such as specific modules for health professionals and citizens (known as *eReporting*). As a result, citizens can report any suspected event associated with any medicine or vaccine. In addition, VigiMed is an open database, and any citizen can search reported adverse events to different products at the following link: https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas/notificacoes-de-farmacovigilancia.

The searchable VigiMed database includes all reports received since January 2018. However, reports submitted directly to some states before the national integration of the Brazilian PV system in 2018 and reports in the NOTIVISA database have not yet been added to VigiMed. As of February 2022, VigiMed contained more than 98,000 reports collected. The leading state in terms of reporting volume is São Paulo (accounting for 20 percent of all Brazilian reports).[23]

[23] ANVISA, "Notificações de farmacovigilância," https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas/notificacoes-de-farmacovigilancia.

Figure 3 Origin of the Reports of Suspected Adverse Effects of Medicines Uploaded in VigiMed



Note: PV = pharmacovigilance; WHO PIDM = World Health Organization Program for International Drug Monitoring.

The new structure of ANVISA

In December 2021, a new resolution (RDC 585/2021) was approved. This resolution established a new structure for ANVISA, which affects PV, among other activities. As a result, GFARM was dissociated from the managing body of products subject to health monitoring and became a direct part of the ANVISA's General Management (Fifth Directorate, *Quinta Direitoria*). This movement aims to strengthen all actions related to the monitoring of medicines and vaccines.[24]

Also, on April 8, 2022, an international PV technical advisory board (*Câmata Técnica de Farmacoviglância*) was constituted[25] with the aim of proposing improvements to Brazilian PV informed by best international best practices and integrating working groups to contribute developing specialized topics.

Additionally, with the goal of strengthening and modernizing PV teaching and research in Brazil, ANVISA asked for letters of expression of interest from universities, teaching hospitals, and research institutions with the aim of selecting the best proposals and funding them with grants.[26]

[24] ANVISA, "Publicado novo Regimento Interno da Anvisa," online article (December 17, 2021), https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/publicado-novo-regimento-interno-da-anvisa.

[25] *Ministério da Saúde/Agência Nacional de Vigilância Sanitária/5ª Diretoria*, "Portaria Nº 222, de 8 de Abril de 2022," publicado em: 13/04/2022 | Edição: 71 | Seção: 2 | Página: 52, gov.br (online), https://www.in.gov.br/web/dou/-/portaria-n-222-de-8-de-abril-de-2022-392944816.

[26] ANVISA, Solicitação de Manifestação de Interesse No 01/2022 (Incentivo ao Ensino, à Pesquisa e ao desenvolvimento de ações de Farmacovigilância no Brasil) (May 5, 2022), https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2022/anvisa-investe-no-fortalecimento-e-na-modernizacao-da-farmacovigilancia/manifestacao-de-interesse.pdf.

AEFI Vigilance.

During the COVID-19 pandemic and the emergency approval of vaccines, the monitoring of safety and the appearance of AEFIs (adverse effects following immunization) become a challenge for PV systems. In many countries this was a challenge for the pre-existing PV teams. This was also the case in Brazil, where the national immunization program had had a small PV team since its creation, even before the consolidation of ANVISA. As a result, ADEs and AEFIs were collected and assessed by different teams; although, in the end, all the reports were uploaded to the Global WHO PIDM database.

In the case of ANVISA, some AEFI reports are received through VigiMed and are analyzed by the PV team. These reports are sent from citizens, the network of sentinel hospitals, and some health professionals. On the other hand, the immunization program has a specific reporting system that uses the *Sistema Unico de Saúde* (Unified Health System, SUS) database, which received AEFI originated in the vaccination wards.

Soon after the onset of ANVISA activities, the Institutional Committee of Pharmacovigilance was created; the GFARM participates in it. Both teams have access to both reporting systems and they are working to make the systems compatible with the Global WHO-PDIM database.

That separation of identification, reporting, and assessment systems for ADEs and AEFIs is not new and, additionally, is common in many countries. It even was reflected in the structure of WHO until 2021, when medicines and vaccines safety teams that had been separate until that time were merged into one team dealing with pharmacovigilance and the safety of medicinal products in the Regulation and Prequalification (RPQ) department.[27] Hopefully, countries will mirror this merger soon.

[27] WHO, "2021 ACSoMP Recommendations," October 26–28, 20201, https://www.who.int/publications/m/item/2021-acsomp-recommendations.

5. Strengthening PV and reducing underreporting

It is well-known that one of the most important problems undermining PV activities is underreporting; this is a common challenge in many countries. To tackle the challenge in Brazil, ANVISA, in collaboration with the state-level CVSs across the country, launched two initiatives to increase reporting capacity.

The Sentinel Network (*Rede Sentinela*) – An example of active PV

As explained earlier, ANVISA is responsible for Brazil's health surveillance at the national level and also the municipal and state health surveillance centers. ANVISA decides which products receive marketing authorization in Brazil. It also has the legal authority and obligation to withdraw marketing authorization if a product's use in clinical practice shows any problems related to its safety or efficacy. Marketing authorization is granted after an evaluation process that collects and reviews the available evidence for each new candidate product (usually from the results of clinical trials). This pre-marketing evidence is generated based on the experiences of a limited number of exposed individuals; so, this evaluation to grant the marketing of a new medical product does not necessarily ensure safety for all. In fact, safety issues are typically detected during large-scale exposure to new products, so some adverse effects may not be discovered until after marketing authorization is granted—a major reason post-marketing surveillance is essential. PV is the most common method of post-marketing authorization surveillance. But to effectively analyze post-marketing safety and efficacy, it is crucial to have data. Unfortunately, in daily practice in Brazil, it is quite difficult to obtain complete and high-quality data describing the outputs of medicines and vaccines needed for such safety surveillance and regulatory decisions.

Many factors lie behind the scarcity of good quality data, including underreporting by health professionals, which is common in Brazil (as it is in other countries) for a variety of reasons. To overcome this reality, ANVISA created *Rede Sentinela* (the Sentinel Network), an interesting and quite unique solution based on active surveillance conducted by a sample set of hospitals dispersed across Brazil's 26 states.

Rede Sentinela's pilot phase (2002–04), included a strong focus on training for medical doctors, nurses, pharmacists, and engineers (because of their responsibility for maintenance at some installations). In each selected hospital, a Health and Hospital Risk Management Team (*Gerencia de Risco*, GR) was designed, and all participants were trained and continuously updated. Around 2,000 health professionals were trained in risk detection and basic epidemiology during this period.

Participating hospitals were selected through a process conducted by ANVISA with support from the ministries of health and education (reflecting the fact that these facilities were training facilities). Invitations to participate in *Rede Sentinela* were sent to a limited number of large and medium-sized training hospitals that conduct clinical procedures involving varied and complex medical technologies. The number of invited hospitals per state also reflected the proportion of medical residency positions offered in each state.

Ninety-six hospitals were involved in the pilot phase, and 91 successfully established a GR. They all delivered the requested products according to their terms of reference signed with ANVISA. The financial resources were used to acquire computers and material for the GR office, payment of *pro-labore* activities, and dissemination material. Adherence to the networks is voluntary, it depends on the hospital decision and does not entail any transference of money from ANVISA.

In most cases, the GR coordinators were already hospital staff; so, their work responsibilities were modified to cover the sentinel activities, including maintaining integrated information systems for technovigilance, hemovigilance, pharmacovigilance,

and technical complaints. Up to 60 percent of the participant hospitals reported online to one or more of the four information systems. From 2002 to 2003, the four systems received a total of 2,158 reports, including 230 documenting ADEs. In the following years, the number of ADE reports kept growing: with 798 in 2004 and 969 in 2005.[28, 29]

The good results of the pilot phase led to a five-year grant (ANVISA/PNUD04/010) that lasted until 2009. The aim was to ensure an improvement of the quality of the health products and a better quality of the provided healthcare. During this second phase, the Sentinel Network admitted interested centers. It involved 221 accredited institutions, corresponding to 3 percent of Brazilian hospitals and covering 24 of Brazil's 27 federative units: of which 56 percent were large hospitals and 24 percent were medium-sized hospitals, with small hospitals accounting for the rest. Among the 50 federal university hospitals involved, 23 joined the Sentinel Network, from which 19 were administered by the Brazilian Hospital Services Company (EBSERH). Within the network, there were 161 general hospitals and 60 specialized institutions. It is noteworthy that 126 institutions of the Sentinel Network were certified as teaching hospitals, representing 64 percent of hospitals certified by the Ministry of Education.[30]

After 2009, ANVISA started taking steps to enhance the continuity and sustainability of the network and to expand it. In 2011, ANVISA published criteria for the recognition of a GR. And in 2014, two regulations were promulgated that provide an additional legal framework for the network's activities and the commitment of the health professionals involved. It is important to highlight that joining the Sentinel Network is a voluntary decision by the health institution, and it does not entail direct transference of financial resources from ANVISA.[31]

The sentinel network is an interesting strategy to promote pharmacovigilance within a wider health surveillance framework. As it involves hospital facilities, the monitoring activities focus on more severe patients than those usually attending primary healthcare centers. It is a low-cost strategy to disseminate healthcare surveillance concepts and to enable ADE identification through either spontaneous reporting or active surveillance of specific suspicions or signals. The deployment of such a complex network is necessarily slow; it requires time to spread the word, engage health professionals, reduce underreporting, and to be able to conduct quick surveys as required by ANVISA. Notwithstanding this, the activities conducted to date certainly have influenced the reporting rate to VigiMed.

Reporting pharmacies – joining efforts to increase reporting rates

In 2005, ANVISA and the CVS of São Paulo state established the pilot project *Farmácias Notificadoras* (Reporting Pharmacies) in coordination with the state association of pharmacists. The aim of the program is to:[32]

- Widen the sources reporting suspected ADE and quality complaints (i.e., lack of efficacy, use of medicines for non-authorized indications, intoxication, drug-drug interactions, drug-food interactions)
- Contribute to the early identification of signals and public health risks suggested by previously unknown adverse reactions
- Improve the quality and number of reports by community pharmacists

Initially, 43 pharmacies (out of a total of 14,000) aimed to increase the number of qualified spontaneous

[28] ANVISA, "Rede Sentinela," archived webpage, https://www.anvisa.gov.br/servicosaude/hsentinela/historico.htm.

[29] ANVISA, "Rede Sentinela," gov.br (October 13, 2020), https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/rede-sentinela/rede-sentinela-1.

[30] Renata Soares de Macedo and Elena Bohomol, "Análise da estrutura organizacional do Núcleo de Segurança do Paciente dos hospitais da Rede Sentinela," *Revista Gaúcha de Enfermagem* (2019) 40 (spe.), e20180264, https://doi.org/10.1590/1983-1447.2019.20180264.

[31] ANVISA, "Rede Sentinela," gov.br (October 13, 2020).

[32] Conselho Regional de Farmácia do Estado de São Paulo, webpage, http://www.crfsp.org.br/67-farmacias-notificadoras/farmacias-notificadoras/276-farmacias-notificadoras.html.

reports of ADEs and quality deviations in medications.[33] Additionally, for public and private pharmacies, belonging to this network is an added value, which entails going beyond commercial activity and getting involved in patient care and public health.

To become part of the reporting pharmacies network and obtain the badge that accredited pharmacies receive as such, there are a few requisites and pharmacies must accede to the requirements of ANVISA and the Pharmacists Association. Examples of requisites include attending training activities and the requirement that at least one pharmacist must remain in the establishment while it is open.[34]

This project was later expanded to other states of Brazil, but 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 project's development; and (iii) covering promotion of safe and rational drug use in the Community Pharmacy context.[35]

In 2015, 3,000 pharmacies adhered to the program in 16 states and 800 cities. International experience in PV has already shown that the number and quality of the collected reports depend on the knowledge that potential reporters have about the PV program and how it works, as well as periodic stimulation of the reporting obligation and actively sharing feedback about medicines safety and identified signals. As a result, the wider the reporting pharmacies network and the more pharmacists involved, the better the efficiency of the program.

In addition, ANVISA reported that 7,000 pharmacists had been trained to identify and report suspected ADEs.[36] The program continues, and it is expected that the reports collected through these pharmacies will contribute to the new VigiMed database.

The incentives to participate are the public acknowledgement of their involvement in the network, as well as training in medicines safety issues.

[33] Daniel Marques Mota, Álvaro Vigo, and Ricardo de Souza Kuchenbecker, "Evolução e elementos-chave do sistema de farmacovigilância do Brasil: uma revisão de escopo a partir da criação da Agência Nacional de Vigilância Sanitária," *Cadernos de Saúde Pública* (2018) 34(10), https://doi.org/10.1590/0102-311X00000218.

[34] ANVISA, "Anvisa estabelece novas diretrizes para o Programa Farmácias Notificadoras," web posting (June 25, 2015), https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/anos-anteriores/anvisa-estabelece-novas-diretrizes-para-o-programa-farmacias-notificadoras.

[35] D.M. Mota, Á Vigo, and R.S. Kuchenbecker, "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) 11:34(10):e00000218. English, Portuguese, https://doi.org/10.1590/0102-311x00000218; erratum in: *Cad. Saúde Pública* (2018) 20:34(12):eER000218, PMID: 30328994, https://doi.org/10.1590/0102-311XER000218.

[36] Portalfarma, "Anvisa estabelece novas diretrizes para o Programa Farmácias Notificadoras," web posting (June 25, 2015), https://pfarma.com.br/noticia-setor-farmaceutico/eventos-farmaceutico/425-diretrizes-programa-farmacia-notificadora.html.

6. Conclusions and take-home messages

To roll out a national pharmacovigilance program, it is essential to have political will, a regulatory framework, a well-trained team of experts in medicines safety, and also the active involvement of health professionals, manufacturers, and citizens, to report suspected adverse events. In addition to these elements, which are common to any country, deploying PV in a very large and middle-income country such as Brazil with a federative structure, more than 200 million inhabitants, and strong differences between the states, requires additional efforts and a few imaginative proposals.

Brazil was admitted as a full member of the WHO PIDM program in 2004. But PV had started at least one decade before, as un-networked activities mostly linked to academia and state health surveillance centers. This basal work is essential to start raising awareness about the safety of medicines and to train the local experts who will inspire the program once the regulatory aspects allow national dissemination.

A particularity in Brazil was the creation and consolidation of a national health surveillance agency structurally and politically independent from the ministry of health. ANVISA deals with different aspects of health monitoring, including the authorization and safety of medicines. This allowed the linking of PV with other monitoring programs such as hemovigilance and surveillance of medical supplies.

Among other initiatives, the Sentinel Hospital Network is especially relevant. Because of the dimensions of the country, it was decided to prioritize surveillance focusing on a group of hospitals across the country, which act as observers of what is happening. Focusing on hospitals means observing conditions that are serious (thus avoiding overwhelming the system with mild and unimportant reports). This network balances the reports sent by the manufacturers and those sent by consumers, which always contain fewer clinical details and lack the necessary context for the appropriate assessment of the reports.

Almost two decades after the admission of Brazil has a full member of the WHO PV program, the country has a PV database fully compatible with the WHO requisites and binding together the activities of the health surveillance centers of all the states. Health professionals, manufacturers, and consumers contribute to the PV Program, and the database is fully accessible.

Take-home messages.

- The PV program in Brazil has been shaped by the geographic and demographic magnitude of the country as well as its federal administrative structure, which is organized in 26 states and the *Distrito Federal* (Federal District).
- Before the regulatory creation of the Brazilian Medicines Agency (ANVISA) in 1999, university departments, societies of health professionals, and citizen movements were already advocating to promote health surveillance and the appropriate and safe use of medicines.
- During ANVISA's consolidation period (2000–09), different PV initiatives were pioneered at the state level, especially in São Paulo. For example, the PV team working in the Health Surveillance Centre of São Paulo was the first to build a PV database and regulate important aspects such as compulsive reporting for the manufacturers.
- The Sentinel Network (*Rede Sentinela*) is an active PV initiative started by ANVISA, involving hundreds of hospitals across the country that act as permanent observatories of different aspects related to the safety of medicines and health technologies. The Reporting Pharmacies Network also contributed to this development. This network has helped consolidate PV across the country, strengthening health professionals' knowledge of safety monitoring activities.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