A comparative analysis of the pharmacovigilance systems of Brazil, Spain, the European Union and the United States based on the information provided by their regulatory agency websites

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Abstract

Background Pharmacovigilance (PV) plays an essential role in monitoring and raising awareness of adverse drug reactions (ADRs). Increasingly, ADRs are reported and PV information and activities are circulated via the Internet. PV actions are carried out by the Regulatory Agencies (RAs) responsible for medicinal products in each country.

Objective The objective of this study is to ascertain and assess the operation and areas of competence of the PV system in Brazil and to compare them with those of Spain, the European Union (EU) and the United States (USA), through the information available on the websites of the RAs in each country.

Methods A search of the information provided on the websites of these countries' RAs, establishing indicators to assess how far the information is available and accessible.

Results The RAs we studied are similarly organised and they complied with most of the 38 indicators we defined to obtain and assess the information they provide on PV procedures and their systems for electronic reporting of ADRs. Brazil's RA, ANVISA, complied with 100% of the areas of competence analysed and with 92.11% of the indicators established for the study.

Conclusions Brazil's PV system, through ANVISA, achieves a good level of performance, both in itself and compared to the other RAs. There is room for improvement in three of the indicators analysed.

Keywords Pharmacovigilance · Regulatory agencies · Website information · Public health · Adverse drug reactions

Introduction

The development of medicinal products was a great advance in medicine, and they have undeniably contributed to improving public health. They are also a source of risk, due to ADRs, which can be of varying degrees of severity, ranging from mild reactions requiring no additional therapeutic measures to fatal reactions that lead, directly or indirectly, to the death of the user. [1–4] It was precisely the worldwide ADRs caused by thalidomide, in 1961, that led the World Health Organization (WHO) to set up the Programme for International Drug Monitoring (PIDM) in 1968, to enable countries to pool information on ADRs. The PIDM currently includes more than 150 countries and has had an increasing influence on public health decisions and on the development and implementation of PV systems. National authorities and/or PV centres have been created, and these act as RAs,

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responsible for promoting and developing PV activities and ensuring that ADR reporting systems work properly, mostly via the Internet. They also transfer these reports to the VigiBase™ global database. [5–7]

The Internet has enabled countries to cooperate more effectively in reporting ADRs and has helped RAs to make decisions on the use of medicines at national and global level. It is also a tool that enables each RA to make more information on PV accessible and available to professionals and members of the public and to provide drug information and control, rapid and safe access to ADR reporting systems, etc. By doing so, it makes the RA's operation and responsibilities more transparent.

This study is part of a doctoral research project currently being conducted by the first author under the supervision of the last author, comparing the PV systems in Brazil and Spain. Its objective is to determine and assess how the PV system operates in Brazil and what its areas of responsibility are, compared with those of Spain, the EU and the US. We include the last two because of the influence they have had, and continue to have, on the development of PV systems in Europe and Latin America, respectively. The study therefore analyses and assesses the PV systems in these countries through their RAs: the National Health Surveillance Agency (ANVISA) in Brazil, the Agency for Medicines and Medical Devices (AEMPS) in Spain, the European Medicines Agency (EMA) in the EU, and the Food and Drug Administration (FDA) in the USA. [8–11].

Methods

To achieve this objective we tried, firstly, to determine each RA's framework of competence and action. We assessed factors such as their creation, purpose, and action in the area of PV. Secondly, we looked to see what information they provide on PV and their established procedures for performing their PV activities. In both cases this was done by carrying out a search of each agency's website between November 2017 and January 2018.

We searched for the information on each RA's website using the RA's own search engine. When occasional difficulties arose, we used Google, making direct reference to the search topic so as to obtain information that would enable us to reach the appropriate link on the RA website.

Determining the framework of competence

We determined the framework of competence and action for each RA on the basis of information in the following areas: territorial range of the RA, location of headquarters, legal form, highest decision-making authority, the year PV activities started in the country, the name of the PV system or

programme, the coordinating body for that system, the existence of an electronic ADR reporting system, the availability of databases with information on ADR reports, and the provision of active surveillance and risk-communication activities on medicinal products by each agency on its website. This enabled us to gain an overview of each RA and to analyse them.

Assessing the information provided on PV

To obtain and assess the information on PV provided by each agency we used the most important indicator models currently available for analysing and assessing a PV system: those of Management Sciences for Health (MSH), the Pan American Health Organization (PAHO), and the WHO. [12–14] The MSH model, published in 2009, was financed by the United States Agency for International Development (USAID). The PAHO model, published in 2010, because of its impact on South American countries, and therefore on Brazil, and that of the WHO, published in 2015, because of its global perspective and because it is the most recent available. Each of these models proposes a series of indicators in a range of areas. The areas are different in each model, but there is some overlap between them (Table 1).

Having analysed these sets of indicators, we concluded that those proposed by PAHO were the most suitable for our purposes. The areas they covered coincided quite closely with our own objectives and areas of interest (legal, organisational and structural issues; established procedures; available resources; the ADR reporting system; and communication and training), and their influence in South America made them especially relevant to Brazil. Therefore, taking the PAHO model as a basis, we checked to see which MSH and WHO indicators were similar, in order to take them into account. We also considered whether these other models contained any further indicators, not included in the PAHO model, that we could incorporate into our study. We excluded indicators referring to processes, results, and public health, since our objective was not to assess the quality of PV systems nor their impact in health terms, but rather the information accessible on the websites.

Consequently, we decided to use the 37 indicators defined by PAHO (100%) and to supplement them with 26 (60%) of the MSH indicators (4 from section 1, 14 from section 2, 6 from section 3 and 2 from section 5), and 18 (26%) of the WHO indicators (all from section A). We grouped them by similarity, resulting in a final total of 38 indicators. We expressed each of these in a simple form that included all the information contained in the corresponding original indicators, to facilitate the subsequent search of the RA websites. Finally, we distributed the indicators in 4 areas: a) legal framework, with 10 indicators, b) organisation, structure and

Table 1 Number of indicators in each model and their distribution by areas of analysis

PAHO		MSH		WHO	
Areas of analysis	No.	Areas of analysis	No.	Areas of analysis	No.
a. Legal framework	10	1. Policy, Law, and Regulation	4	A. Structure	21
b. Directives and guidelines	5	2. Systems, Structures, and Stakeholder Coordination	15	B. Process	22
c. Organization and structure	4	3. Signal Generation and Data Management	6	C. Outcome or impact	20
d. Internal procedures	9	4. Risk Assessment and Evaluation	8	D. Public health	9
e. Human and other resources	4	5. Risk Management and Communication	10		
f. Records and results	4				
g. Availability of information	1				
Total	37	Total	43	Total	72

procedures, with 18, c) resources, with 4, and d) communication and training, with 6 (Table 2).

Results

Framework of competence and action of each regulatory agency

The essential role of the RAs analysed, ANVISA, AEMPS, the EMA and the FDA, is to ensure public safety in the use of medicinal products through a range of actions. In the area of PV, these include managing suspected ADR reports, conducting post-authorisation studies, managing databases of suspected ADR reports, training, and distributing product safety reports and data sheets.

Brazil's PV system is coordinated by the National Drug Monitoring Centre (CNMM in Portuguese), based in ANVISA. The General Management for Monitoring Products Subject to Healthcare Vigilance (GGMON in Portuguese), a unit of ANVISA, coordinates the electronic ADR reporting system, called NOTIVISA (Healthcare Surveillance Reporting System), and also active surveillance through the Sentinel Hospital Network. Both of these are strategies of the Healthcare Surveillance Reporting and Investigation System (VIGIPOS). [15–19] In Spain, AEMPS coordinates the Spanish Pharmacovigilance System for Medicinal Products for Human Use (SEFV-H). This consists of AEMPS itself, the competent bodies of the Autonomous Communities in the area of PV, the PV units or centres in each Autonomous Community, healthcare professionals, and the public. AEMPS also manages NOTIFICARAM (Notification of Suspected Adverse Drug Reactions). [20–22] In the EU, the EMA coordinates the European PV system, providing information on the safe and effective use of medicines. It also manages and maintains EudraVigilance, the European system for managing and analysing information on suspected ADRs associated with medicinal products

authorised in the European Economic Area (EEA). At the same time, each member state of the EU has its own national regulatory agency which develops its PV measures at national level within the framework of the EMA and European law. [23–25] The PV system in the USA is coordinated by the FDA; it was the first country to have specific drug safety regulations and has one of the most rigorous legislative regimes on the safety of medicinal products. This is based on passive and active vigilance activities. The passive vigilance includes the FDA Adverse Event Reporting System (FAERS), and notifications, via the MedWatch program, are made spontaneously by health professionals and members of the public and on a mandatory basis by the pharmaceutical industry. [26–30]

Our analysis of the framework of competence and action of the RAs took account of the areas of analysis we had defined. All the information was obtained from the website of each agency (Table 3).

The results in Table 3 show that most of the information on the areas analysed is available from the websites. The exceptions are that the EMA does not have a system for direct reporting of suspected ADRs, since this is done through the agencies of each EU country, and AEMPS does not have an active surveillance system of its own or one that it coordinates.

Information on PV provided by the RAs

To assess the information on PV provided by the EMA, AEMPS, the FDA and ANVISA, we analysed each agency's website to determine how it responded to each indicator in Table 2. If the information was available, the response was YES, and if it was not present, the response was NO (Table 4).

The agencies, taken together, complied with the majority (86.84%) of the 38 indicators (three or four positive responses signified compliance). The results for individual agencies show that AEMPS and the FDA achieved the highest level of compliance, 94.74%, followed by ANVISA, with 92.11%, and that the lowest was that of the EMA, with 78.95%. The

Table 2 Proposed indicators: relationship with indicators in each model

Indicator		Indicator code in model		
No.	Definition	PAHO	MSH	WHO
a. Legal Framework				
1	There is a legal provision/policy document on drug safety	1.1	1.1	CST2
2	There is specific legal provision on PV and implementation of a surveillance system	1.2	1.2	
3	There are legal provisions for Marketing Authorisation Holders (MAHs) on PV and drug safety, particularly safety studies	1.3 2.3	1.4	ST11
4	There are legal provisions requiring manufacturers, distributors, importers and exporters to report ADRs to the national regulatory authority	1.4	1.3	
5	There are legal provisions stipulating that health professionals have to report ADRs to the national regulatory authority or to MAHs	1.5	1.2	
6	There are specific requirements on the reporting of safety matters for specific categories of products (vaccines, biological products, etc.)	1.6	1.1	
7	There are specific requirements that MAHs, manufacturers, distributors or wholesalers must comply with concerning the appointment of a person responsible for post-marketing safety surveillance	1.7 2.4	1.3 1.4	
8	The terminology and classification to be used for the various types of ADRs are formally specified	1.8 2.2	1.4	
9	The deadlines for reporting ADRs are formally specified	1.9 2.5	2.7	
10	There are specific requirements that health institutions must comply with concerning the appointment of a person in charge of post-marketing safety surveillance	1.10 2.4	2.7	
b. Organisation, Structure and Procedures				
11	There are procedures for post-marketing safety monitoring	2.1	3.2	
12	There is a national drug regulatory authority responsible for formally regulated pharmacovigilance	3.1	2.1 2.2	CST3
13	There are decentralised centres and/or units responsible for pharmacovigilance and drug safety		2.1	CST1
14	Activities devolved to other agencies or authorities follow the same standards, guidelines and procedures	3.2	2.7	
15	There are mechanisms that ensure cooperation and collaboration with and between the decentralised organisations	3.4 3.3		
16	The agency is a full or associate member of the WHO Collaborating Centre (UMC) in Uppsala		2.15	
17	The information sources and external reference materials are available for decision-making on ADRs and safety surveillance	4.1	3.1	ST3
18	There are databases available to provide information on medicines, including, where applicable, a service for asking questions and answering queries, to ensure rational use of medicinal products		2.11	ST2 ST4
19	There is a computerised system for managing ADR reports		2.9	ST5
20	There is a standard ADR report form, as well as registration and assessment procedures	4.2	3.3	CST6 CST7
21	There are fields on the form for reporting suspicions about drug quality (or on a separate form)		3.4	
22	There are fields on the form for reporting suspected medication errors (or on a separate form)		3.5	CST6
23	There are fields on the form for reporting therapeutic ineffectiveness (or on a separate form)		3.6	CST6
24	There are fields on the form for reporting suspected counterfeit drugs/drugs that do not comply with the requirements (or on a separate form)			CST6
25	There are procedures for detecting and prioritising signals in relation to their impact on public health and for analysing safety trends	4.4 4.3		
26	There are standardised operational procedures for activities to ensure their execution and quality, involving the national regulatory authority and relevant stakeholders	4.7 4.5 4.6	2.8 2.14	ST8
27	Informative and educational campaigns on pharmacovigilance and use of medicines are regularly organised	4.8	5.9	
28	There is an ADR report form for the general public	4.9	3.3	CST6

Table 2 (continued)

Indicator	Indicator code in model		
	PAHO	MSH	WHO
No. Definition			
c. Resources			
29 There are staff responsible for pharmacovigilance or drug safety activities	5.1	2.4	CST5
30 There are established quality procedures	5.2		
31 There is a consultative committee that advises the national regulatory authority on drug safety	5.4	2.6	CST10
	5.3		
32 There is an annual budget available for the operation of the national regulatory authority		2.5	CST4
d. Communication and Training			
33 The information collected on safety is used to adopt or modify regulatory decisions on new marketing authorisations	6.1	5.2	
34 The information/database on safety events reported and actions taken is maintained	6.2		ST4
	6.3		
35 The database enables the national regulatory authority to evaluate and interpret safety signals	6.4	2.9	
36 There is a newsletter and/or active website for periodic circulation of information on pharmacovigilance		2.10	CST9
37 Training aimed at health professionals, the public and other stakeholders is promoted and/or organised		2.13	ST9
38 Information on ADRs and on the safety surveillance measures adopted is communicated to the public, including alerts	7.1	2.3	
Total	37	26	18

number of indicators not complied with was 3 for ANVISA (7.89%), 2 for AEMPS and the FDA (5.26%), and 8 for the EMA (22.05%). Focusing on the areas in which the indicators are distributed, the greatest divergences between RAs occur in the legal framework and in organisation, structure and procedures; there are fewer differences in communication and training, and none in resources (Table 5). The divergence in the legal framework is focused, on the part of the EMA and the FDA, on the non-existence of obligation to have a person responsible for post-marketing surveillance of medicines on MAHs, manufacturers, distributors, etc., nor in the health institutions and centres, and the part of the EMA and ANVISA, in the non-existence of obligation that producers, distributors, etc., to report information they may have on suspected ADRs. The divergence in the area of organisation, structure and procedures is concentrated in the fact that the information obtained from AEMPS and the EMA suggests a lower level of requirement for submitting information through forms on some issues, such as therapeutic inefficacy and quality, than in the case of the FDA and ANVISA.

Discussion

This study is relevant for establishing and assessing the nature of the PV system in Brazil and how it works compared with the Spanish system, and also with those of the USA and the EU, which have had and continue to have such an influence on the Brazilian and Spanish systems. It also enables us to establish whether these agencies have different or similar

patterns of organisation and action in the area of PV, so that we can assess them in relation to internationally recognised parameters and standards.

In terms of its framework of competence ANVISA is comparable with AEMPS, and also with the EMA and the FDA, since although it is the newest of the four, having been founded in 2001, it contains all the elements of the other systems and RAs. Indeed, having an active adverse event surveillance system puts ANVISA in a better position than AEMPS, which does not have or coordinate a sentinel network of its own. The EMA has no electronic ADR reporting system directly accessible to professionals and members of the public, as it is a coordinating agency for the PV system of the EU and the EEA. Access to electronic ADR reporting systems is at member state level, although all of them are integrated into the European EUDRAVIGILANCE database.

As for the information on PV provided by the websites, the responses listed in Table 4 and the summary in Table 5 show that all the RAs comply with most of the indicators. However, a comparative analysis of ANVISA in relation to AEMPS, as well as to the EMA and the FDA, reveals differences which merit comment and analysis. ANVISA does not comply with three indicators, 4, 35 and 37, which AEMPS and the FDA do comply with; the EMA does not comply with indicator 4 and does comply with 35 and 37.

Indicator 4, to which the response was NO for ANVISA and YES for AEMPS and the FDA, asks whether it is compulsory for all interested parties to report information they may have on suspected ADRs. This is not the case in Brazil, and it would therefore be beneficial for this to be corrected so

Table 3 Framework of competence of the RAs (ANVISA, AEMPS, EMA, FDA): information obtained from their websites

Areas of analysis	ANVISA ^a	AEMPS ^b	EMA ^c	FDA ^d
Territorial range	Brazil	Spain	EU and EEA	USA
Current location	Brasilia (Brazil)	Madrid (Spain)	London (United Kingdom) [until end 2018], Amsterdam (Netherlands) [2019]	Washington (USA)
Organisational legal form	Autonomous agency linked to the Ministry of Health	State agency attached to the Ministry of Health, Social Services and Equality	Decentralised agency of the EU	Independent agency linked to the Department of Health and Human Services
Highest decision-making authority	Board of Directors	Board of Management	Management Board	FDA Commissioner
Start of PV activities	2001	1984	1995	1962
Name of the system or programme	Healthcare Surveillance Reporting and Investigation System (VIGIPROS)	Spanish Pharmacovigilance System for Medicinal Products for Human Use (SEFV-H)	EU pharmacovigilance system	FDA Post-Marketing Drug Safety Surveillance
Body with direct responsibility for coordinating PV actions	National Drug Monitoring Centre (CNMM)	Pharmaco-epidemiology and Pharmacovigilance Division	Inspections, Human Medicines Pharmacovigilance and Committees Division	CDER Office of Surveillance and Epidemiology
ADR reporting system	Notification System in Sanitary Surveillance (NOTIVISA)	NotificaRam and Yellow card	The EMA cannot accept ADR reports directly, but only through the national ADR reporting systems	FDA Safety Information and Adverse Event Reporting Program (MEDWATCH)
Spontaneous ADR reporting database	National Pharmacovigilance Database	Spanish Pharmacovigilance Database (FEDRA)	EU data processing network and management system for reporting and evaluation of suspected adverse drug reactions (EUDRAVIGILANCE)	FDA Adverse Event Reporting System (FAERS) Public Dashboard
Active adverse event surveillance	Sentinel network	Information notes, safety warnings, alerts, etc.	Open consultations	Sentinel Initiative
Risk communication	Newsletters, letter to health professionals, alerts.		Latest news, Patients safety, New medicines	Drug alerts, drug safety communications, medication errors, etc.

Note. RA website addresses: ^a www.portal.anvisa.gov.br; ^b www.aemps.gob.es; ^c www.ema.europa.eu; ^d www.fda.gov

Table 4 Compliance with the PV information indicators by the Pharmacovigilance Regulatory Agencies: information provided through their websites

No. Indicator	ANVISA	AEMPS	EMA	FDA
a. Legal Framework				
1 There is a legal provision/policy document on drug safety	YES	YES	YES	YES
2 There is specific legal provision on pharmacovigilance and implementation of a surveillance system	YES	YES	YES	YES
3 There are legal provisions for MAHs on PV and drug safety, particularly safety studies	YES	YES	YES	YES
4 There are legal provisions that requiring manufacturers, distributors, importers and exporters to report ADRs to the national regulatory authority	NO	YES	NO	YES
5 There are legal provisions stipulating that health professionals have to report ADRs to the national regulatory authority or to MAHs	YES	YES	YES	YES
6 There are specific requirements on the reporting of safety matters for specific categories of products (vaccines, biological products, etc.)	YES	YES	YES	YES
7 There are specific requirements that MAHs, manufacturers, distributors or wholesalers must comply with concerning the appointment of a person responsible for post-marketing safety surveillance	YES	YES	NO	NO
8 The terminology and classification to be used for the various types of ADRs are formally specified	YES	YES	YES	YES
9 The deadlines for reporting ADRs are formally specified	YES	YES	YES	YES
10 There are specific requirements that health institutions must comply with concerning the appointment of a person in charge of post-marketing safety surveillance	YES	YES	NO	NO
b. Organisation, Structure and Procedures				
11 There are procedures for post-marketing safety monitoring	YES	YES	YES	YES
12 There is a national drug regulatory authority responsible for formally regulated pharmacovigilance	YES	YES	YES	YES
13 There are decentralised centres and/or units responsible for pharmacovigilance and drug safety	YES	YES	YES	YES
14 Activities devolved to other agencies or authorities follow the same standards, guidelines and procedures	YES	YES	YES	YES
15 There are mechanisms that ensure cooperation and collaboration with and between the decentralised organisations	YES	YES	YES	YES
16 The agency is a full or associate member of the WHO Collaborating Centre (UMC) in Uppsala	YES	YES	NO	YES
17 The information sources and external reference materials are available for decision-making on ADRs and safety surveillance	YES	YES	YES	YES
18 There are databases available to provide information on medicines, including, where applicable, a service for asking questions and answering queries, to ensure rational use of medicinal products	YES	YES	YES	YES
19 There is a computerised system for managing ADR reports	YES	YES	YES	YES
20 There is a standard ADR report form, as well as registration and assessment procedures	YES	YES	YES	YES
21 There are fields on the form for reporting suspicions about drug quality (or on a separate form)	YES	NO	NO	YES
22 There are fields on the form for reporting suspected medication errors (or on a separate form)	YES	YES	NO	YES
23 There are fields on the form for reporting therapeutic ineffectiveness (or on a separate form)	YES	NO	NO	YES
24 There are fields on the form for reporting suspected counterfeit drugs/drugs that do not comply with the requirements (or on a separate form)	YES	YES	NO	YES
25 There are procedures for detecting and prioritising signals in relation to their impact on public health and for analysing safety trends	YES	YES	YES	YES
26 There are standardised operational procedures for activities to ensure their execution and quality, involving the national regulatory authority and relevant stakeholders	YES	YES	YES	YES
27 Informative and educational campaigns on pharmacovigilance and use of medicines are regularly organised	YES	YES	YES	YES
28 There is an ADR report form for the general public	YES	YES	YES	YES
c. Resources				
29 There are staff responsible for pharmacovigilance or drug safety activities	YES	YES	YES	YES
30 There are established quality procedures	YES	YES	YES	YES
31 There is a consultative committee that advises the national regulatory authority on drug safety	YES	YES	YES	YES
32 There is an annual budget available for the operation of the national regulatory authority	YES	YES	YES	YES
d. Communication and Training				
33 The information collected on safety is used to adopt or modify regulatory decisions on new marketing authorisations	YES	YES	YES	YES
34 The information/database on safety events reported and actions taken is maintained	YES	YES	YES	YES
35 The database enables the national regulatory authority to evaluate and interpret safety signals	NO	YES	YES	YES
36 There is a newsletter and/or active website for periodic circulation of information on pharmacovigilance	YES	YES	YES	YES
37 Training aimed at health professionals, the public and other stakeholders is promoted and/or organised	NO	YES	YES	YES
38 Information on ADRs and on the safety surveillance measures adopted is communicated to the public, including alerts	YES	YES	YES	YES

as to enhance the effectiveness of its PV system. Indicator 35 asks whether the database enables the national regulatory authority to evaluate and interpret safety signals. The answer for ANVISA is NO, although its website shows that the database is NOTIVISA. When it is accessed, however, there is no indication that the information needed is available. Considering

that evaluating information on suspected ADRs and detecting signals are essential actions in PV, ANVISA ought to develop a tool to enable this action to be performed. And regarding the response of NO to indicator 37, on whether training is promoted and/or organised, we find on ANVISA's website that there is information on the importance of training, and on

Table 5 Percentage distribution of compliance with indicators by areas and agencies

Indicators by areas	ANVISA	AEMPS	EMA	FDA
a) Legal Framework	90	100	70	80
b) Organisation, Structure and Procedures	100	89	72	100
c) Resources	100	100	100	100
d) Communication and Training	67	100	100	100

some courses offered for health professionals. However, there is no indication that this training is defined and standardised in terms of frequency and organisation for all interested parties, though this would be desirable in order to extend knowledge of PV and related activities.

Turning now to the results obtained by the PV systems and RAs of the countries chosen for comparison, that is, Spain, the EU and the USA, we emphasise once again the distinguishing feature of the EMA, on which we have already commented, which justifies its NO for indicators 4, 7, 10, 16, 21, 22, 23 y 24. In the case of AEMPS, the only indicators it does not comply with are 21 and 23, which refer, respectively, to collecting information on suspicions about drug quality and on therapeutic ineffectiveness of medicines. It would be useful for this information to be available, as it is with ANVISA and the FDA. As for the FDA, the indicators with which it does not comply are no. 7, on whether MAHs, manufacturers, distributors, etc. are required to have a person in their organisation responsible for post-marketing surveillance of medicines, and no. 10, on whether it is mandatory to have such a person in health institutions and centres. It would be fruitful to consider these points, to achieve fuller and deeper involvement of all interested parties in the PV system.

Collecting information through the searches we performed was in general easier and more accessible in the FDA, the EMA and AEMPS and more difficult in the case of ANVISA and the Brazilian PV system. In several cases, even though the information was available, as can be seen in Table 4, it could not be found directly. To locate it we had to use our knowledge of the system itself, or perform an initial Google search, which enabled us to find the information subsequently on the corresponding pages of the ANVISA site. When it is a matter of health professionals, and especially members of the public, being able to find information on PV and access the electronic ADR reporting system, these issues of accessibility should be borne in mind as matters for improvement.

The limitation of the study lies in the objective defined for it, since for this reason it does not address the question of establishing and assessing the effectiveness and operational efficacy of the PV system in each country. Nor does it evaluate the functionality of the system or the results of the information and records on reported ADRs. To achieve these purposes would require another study, which would undoubtedly be of great interest.

Attention should also be drawn to the importance of what a study of this kind reveals about PV, in that a well structured and effectively functioning PV system will clearly contribute to better use and greater efficacy of medicinal products, and consequently to public health. Both these outcomes are the result of ever-increasing engagement and responsibility on the part of pharmacists, along with other health professionals, and of pharmaceutical sciences as a whole.

Conclusions

The study enables us to conclude that ANVISA complies with most (92.11%) of the points measured by the indicators used here, showing that the Brazilian PV system and ANVISA perform well. This is also confirmed by comparison with the other RAs, since while ANVISA fails to comply with three indicators (7.89%), the other RAs (AEMPS and the FDA), with the qualification already explained in relation to the EMA, have two non-compliant indicators (5.26%). Compliance by ANVISA with precisely those three indicators (notification of suspected ADRs by manufacturers, distributors, importers and exporters of medicinal products, availability of a database to evaluate information on suspected ADRs and interpret safety signals, and organised training on a structured and periodic basis reaching all interested parties) would help to still further improve the operation and efficacy of PV in Brazil.

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Authors' contributions All the authors have made substantive contributions to the study and all of them endorse the data and conclusions. All the authors read and approved the final manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Abbreviations ADR, Adverse Drug Reaction; AEMPS, Spanish Agency for Medicines and Medical Devices; ANVISA, Brazilian National Health Surveillance Agency; CDER, Office of Surveillance and Epidemiology; CNMM, National Drug Monitoring Centre; EEA, European Economic Area; EMA, European Medicines Agency; EU, European Union;

EUDRAVIGILANCE, EU data processing network and management system for reporting and evaluation of suspected adverse drug reactions; *FAERS*, FDA Adverse Event Reporting System; *FDA*, Food and Drug Administration (USA); *FEDRA*, Spanish Pharmacovigilance, Adverse Reaction Data; *GGMON*, General Management for Monitoring Products Subject to Healthcare Vigilance; *MAH*, Marketing Authorisation Holder; *MEDWATCH*, FDA Safety Information and Adverse Event Reporting Program; *MSH*, Management Sciences for Health; *NOTIFICARAM*, Notification of Suspected Adverse Drug Reactions; *NOTIVISA*, Healthcare Surveillance Reporting System; *PAHO*, Pan American Health Organization; *PIDM*, Programme for International Drug Monitoring (WHO); *PV*, Pharmacovigilance; *RA*, Regulatory Agency; *SEFV-H*, The Spanish Pharmacovigilance System for Medicinal Products for Human Use; *UMC*, Upsala Collaborating Centre (WHO); *USA*, United States; *USAID*, United States Agency for International Development; *VIGIPOS*, Healthcare Surveillance Reporting and Investigation System; *WHO*, World Health Organization.

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