Brazilian Regulation in Pharmacovigilance: A Review

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Abstract

Brazilian health legislation on drug surveillance has been available for only four decades. This study aimed to analyze the chronological evolution of the pharmacovigilance legislation in Brazil. A critical review of the legislations and communications published between 1976 and 2015 was conducted. Sixty-two (62) documents were identified. Advancements in the assessment of health technologies occurred only after the publication of the National Drug Policy (1998), the foundation of the National Health Surveillance Agency (ANVISA), and the creation of the National Center for Drug Monitoring (2001). From 2009, pharmacovigilance practices became mandatory for marketing authorization holders. Despite recent, the regulatory advancements in pharmacovigilance in Brazil are equivalent to international practices. However, there is still a lack of regulations for biosimilars and veterinary medicines, of agility in reporting non-serious risks to manufacturers and health care services, and of encouragement for reporting technical complaints and quality deviations, which could improve and control post-marketing drug quality. It is necessary to encourage and develop strategies for the decentralization of pharmacovigilance actions to the whole country.

Keywords: Pharmacovigilance; Product surveillance; Post-marketing; Drug information services; Health legislation; Regulation pharmaceutical policy

Introduction

The risk-benefit assessment of drugs is conducted during their whole lifecycle [1,2]. Randomized clinical trials assess the risk-benefit ratio in ideal conditions, where variables such as age, sex, the presence of morbidities or comorbidities, polypharmacy and exposure time to the drug are controlled.

In Brazil, a drug is considered as "new" in the first five years of commercialization. Drug registration is renewed by submitting a pharmacovigilance safety update report and a risk minimization plan [3].

Effective pharmacovigilance measures allow to improve the risk-benefit ratio by providing information about drug safety under real conditions of use [4] that is, on different age groups, in patients with morbidities, comorbidities, and genetic polymorphisms, and after prolonged exposure time to the drug. Cultural differences between countries, the use of traditional medicine (supplementation and medicinal plants) and the different quality standards in the manufacturing process of drug products can also affect drug safety [5]. These variables influence the creation of laws that regulate and monitor the safety, quality and effectiveness of these products.

Pharmacovigilance actions are constantly changing, adding resources to proactively detect drug-related problems. Prevalence data obtained on post-marketing surveillance have been used to identify genetic biomarkers [6,7], aiming to improve the safety and effectiveness of the pharmacotherapy [7].

In this context, this study aimed to assess the Brazilian legislation on pharmacovigilance, in order to identify the conceptual changes and actions in drug post-marketing surveillance over the years.

Methods

A critical review of the Brazilian legislations was conducted using a descriptive study of historical nature [8].

The strategy comprised a search in the legislation database of the Brazilian health authority (National Health Surveillance Agency [ANVISA])–Saude Legis (Health Legislation System) and VISELEGIS (Health Surveillance Legislation System) to identify legislations that regulate pharmacovigilance practice in Brazil. A search was also conducted in the website of the Ministry of Health, in the field "legislation" within "The Ministry", and in the portal of the Federal Government legislation [9]. Another search for legislations was performed in the websites of the Pharmacovigilance Centers of the states of Bahia, Para, Rio de Janeiro, Santa Catarina and Sao Paulo, which were registered at ANVISA’s website [10].

The search was conducted by the type of legislation, with no restrictions to the period, origin, source and situation (revoked or current), and using the following keywords, "drug safety", "marketing authorization holders", "pharmacovigilance" and "patient safety".

The collected material was examined using the content analysis technique, which is a data processing technique used to objectively, quantitatively, and systematically describe the selected content [11].

From the initial reading of the selected material, the following variables were defined: year of publication, scope (federal or state), type of legislation (laws, decrees, resolutions, ordinances and communications), to whom it is applied (industries; health care services; pharmacies and drugstores; regulatory organs and health
professionals), and what it regulates (what should be done by whom it is applied).

During data processing, the content of the texts was analyzed, in order to assess the historical evolution of concepts, competences and responsibilities in pharmacovigilance of each sector involved. We also evaluated whether there are sectors not covered by current regulations in pharmacovigilance.

Results

The Brazilian pharmacovigilance legislation dates from 1976 to 2015 (Table 1). The Health Surveillance Center of the State of São Paulo (CVS-SP) and ANVISA are responsible for regulating and monitoring the pharmacovigilance actions at a state and national level, respectively. The regulated sectors are health care assistance services (Public health care establishments, pharmacies, drugstores, particular clinics and hospitals), drug manufacturers, Marketing Authorization Holders (MAH), and health care professionals (Table 1). Existing policies cover all health care levels (primary, secondary and tertiary levels) and spheres involved in the drug chain. However, there were no relevant legislations on the pharmacovigilance of bio similar and veterinary products.

| Before founding ANVISA (1976-1999) | After founding ANVISA during focused on drug safety (1999-2015) with regulation of actions on products and services that involve risks to health | Focused on patient safety (2013-2015) with regulation of risk communication (ADR and drug interactions) and sets deadlines for reporting |
|---|---|---|
| Law | Level | Enforcer | Regulation | Law | Level | Enforcer | Regulation | Law | Level | Enforcer | Regulation |
| Law No. 6360 | National | MAH | ADR reporting and efficacy assessment | Law No. 9782 | National | ANVISA | To control, monitor, and regulate products and services that involve risks to health | Ord. No. 529 | National | Health care services | Establishes the National Program of Patient Safety to enable promoting the mitigation of the occurrence of ADE in health care |
| Decree No. 79094 | National | MAH | ADR reporting⁵ | Res. No. 328 | National | Pharmacies Drugstores | Risk communication (ADR and drug interactions) | Ord. No. 529 | National | Health care services | Approves an instrument for risk communication |
| Ord. 577 | National | Technical Council | Pharmacological surveillance system (ADR reporting, assessment and record) | Res. No. 33 | State (SP) | CVS-SP | Establishes the Pharmacovigilance Unit | Ord. No. 264 | National | Health care services | Establishes actions for patient safety and risk communication (ADE) and sets deadlines for reporting |
| Federal Constitution | National | State | To ensure safety and prevent health damage | Res. No. 33 | National | Pharmacies | Pharmacovigilance studies | RD C No. 36 | National | Health care services | Establishes the National Program of Pharmacovigilance and the National Program of Patient Safety on medication use |
| Ord. No. 17 | State | Surveillance Center | Establishment of pharmacovigilance system (ADR reporting, assessment and record) | Ord. No. 696 | National | CNMM | To structure post-marketing drug surveillance in Brazilian territory | Res. No. 863 | National | MAH | Post-registration pharmacovigilance reports (stability test) |
| Law No. 8080 | National | Health care services | To identify and prevent health damage | Ord. No. 239 | National | ANVISA | Establishes the Pharmacovigilance Unit | Res. No. 136 | National | MAH | Renewal of registration of new drugs by submitting a pharmacovigilance report |
| Res. No. 300 | National | Hospitals | Establishes the hospital pharmacovigilance system | Res. No. 138 | National | MAH | Renewal of registration of new drugs and classification of the sales category according to RDC No. 53 | Res. No. 72 | State (SP) | CVS-SP | Establishes a post-marketing drug surveillance program |
| Res. No. 132 | State (SP) | CVS-SP | Creation of a Commission of Iatrogenic Control | Res. No. 138 | National | MAH | Renewal of registration of new drugs and classification of the sales category according to RDC No. 53 | Res. No. 132 | State (SP) | CVS-SP | Establishes the period of 180 days after the publication of the RDC No. 36 for implementing |
| Law | Level | Enforcer | Regulation | Law | Level | Enforcer | Regulation |
|-----|-------|----------|------------|-----|-------|----------|------------|
| Ord. No. 3916 | National | HM | To ensure drug safety and efficacy and the rational use of drugs through pharmacovigilance | Ord. No. 23 | State (SP) | Pharmacies | Pharmacovigilance data |
| Ord. No. 6 | National | HM | Establishes an instrument for risk communication (ADR) of drugs subject to special control. Establishes an instrument for risk communication (ADR) of retinoids | Ord. No. 24 | State (SP) | Health care services | Establishes an instrument for risk communication (ADR) and provides deadlines for reportinga |
| Res. No. 91 | National | MAH | Post-registration pharmacovigilance reports of phytotherapics (stability) |
| Ord. No. 4 | State (SP) | Pharmacies Drugstores | Risk communication (ADR) associated with clozapinea |
| Ord. No. 8 | State (SP) | Health care services | Establishes an instrument for risk communication (ADR) and provides deadlines for reportinga |
| Ord. No. 3 | State (SP) | CVS-SP | Creates the Pharmacovigilance Center of the CVS-SP |
| Ord. No. 4 | State (SP) | Health care services MAH user | Updates and establishes an instrument for risk communication (ADR) and DQD. Stipulates deadlines for reportinga |
| RDC No. 233 | National | MAH, distributors importers | Pharmacovigilance study |
| RDC No. 315 | National | MAH | New biological products post-registration pharmacovigilance report |
| Law          | Level | Law          | Level | Law          | Level | Law          | Level | Law          | Level | Law          | Level |
|--------------|-------|--------------|-------|--------------|-------|--------------|-------|--------------|-------|--------------|-------|
| Res. No. 2697 | State (RJ) | Health Department | Creates the Pharmacovigilance Program and establishes an instrument for risk communication |
| Res. No. 398  | State (RJ) | Health care services | Encourages ADE risk communication of Hexabrix 320<sup>a</sup> |
| Ord. No. 95 | National | ANVISA | Establishes the Coordinating Committee of Actions for the Rational Use of Drugs |
| Res. No. 39   | National | ANVISA CRF | Establishes the Advisory Committee of the Notifying Pharmacy Program |
| RDC No. 16    | National | MAH | Post-registration pharmacovigilance report (ADR and efficacy) for generic drugs<sup>a</sup> |
| RDC No. 17    | National | MAH | Pre and post-registration pharmacovigilance reports for similar drugs |
| Ord. No. 92   | National | Anvisa Health Surveillance Secretariat National Quality Control Institute of Oswaldo Cruz Foundation | Vaccines and Other Immunobiologicals Pharmacovigilance Program in the scope of the Single Health System |
| Ord. No. 113  | State (SP) | CVS-SP | Determines precautionary prohibition of lumiracoxib due to accumulation of serious ADR reports<sup>a</sup> |
| Ord. No. 286  | State (SP) | CVS-SP | Prohibition on marketing of rimonabant due to accumulation of serious ADR reports<sup>a</sup> |
| Law | Level | Law | Level | Law | Level | Law | Level | Law | Level |
|-----|-------|-----|-------|-----|-------|-----|-------|-----|-------|
| RDC No. 4 | National | MAH | Provides for pharmacovigilance standards |
| RDC No. 44 | National | Pharmacie\'s Drugstores | ADE and technical complaints reporting |
| NI No. 14 | National | MAH | Approves the Pharmacovigilance Guidelines for implementing the RDC No.4 |
| Ord. No. 3252 | National | Health Ministry | Funding of Health Surveillance actions, such as the Notifying Pharmacy Program, Sentinel Hospitals and Notivisa, by the Union, the States, the Federal District and Municipalities\(^a\) |
| Ord. No. 1660 | National | ANVISA | Establishes the Health Surveillance Reporting and Investigation System - VIGIPOS, responsible for monitoring, analyzing and investigating adverse events and technical complaints |
| RDC No. 67 | National | MAH | Establishes the general requirements of technical surveillance\(^a\) |

\(^a\) Funding of Health Surveillance actions, such as the Notifying Pharmacy Program, Sentinel Hospitals and Notivisa, by the Union, the States, the Federal District and Municipalities.
| Law   | Level | Law | Level | Law   | Level | Law | Level | Law   | Level | Law   | Level |
|-------|-------|-----|-------|-------|-------|-----|-------|-------|-------|-------|-------|
| Based in the State of São Paulo in the online reporting system - PERIWEB |
| RDC No. 7 | National | Hospital (ICU) | Risk management and ADE communication; risk minimization plans and reporting to the risk management |
| RDC No. 57 | National | Blood center | Risk communication (ADR) associated with transfusion |
| RDC No. 52 | National | MAH and health care services | Prohibition of manufacturing, importing, exporting, distributing, manipulation, prescribing, dispensing, providing, trading and using drugs or drug formulations containing the substances amfepramone, fenproporex, and mazindol, their salts and isomers, as well as intermediates |
| Ord. No. 1 | State (SP) | Health care services | Risk communication (ADE) related to the use of clozapine |
| Res. 54 | State (SP) | CVS-SP | Approves the Pharmacology Committee of the Health Department of the State of SP, which will implement actions and pharmacovigilance |
| Ord. No. 1378 | National | Health care services | Risk communication (ADR) related to vaccines |
| Law | Level | Law | Level | Law | Level | Law | Level | Law | Level | Law | Level |
| Decree | National | MAH | Risk communication |
Brazilian pharmacovigilance regulations have been available for less than 50 years, but there was a significant advance in pharmacovigilance in Brazil. Before the 1990s, Brazil already had legislations for assessing drug safety aiming to detect adverse drug reactions (ADR). However, their implementation was considered unsuccessful [12], since the responsibility for pharmacovigilance practices was mainly of MAH. Also, safety assessment was not compulsory or monitored by national authorities at that time.

Strategies to enhance ADR and drug intoxication reporting started to be developed in the 1990s, when the CVS-SP first included educative interventions for health professionals and drug risk communication reporting as attributions of the pharmacovigilance practice.

The expansion to the whole national territory took place nine years later, with the publication of the National Drug Policy, the foundation of ANVISA, the inclusion of Brazil as a member of the World Health Organization’s (WHO) International Drug Monitoring Programme, and the creation of the National Center for Drug Monitoring (CNMM). At this point, pharmacovigilance activities were...
systematized, by developing tools describing how, when, and why to report; establishing deadlines for serious and non-serious adverse drug events (ADE) reporting; and developing strategies to minimize underreporting.

In 2002, the WHO widened the scope of pharmacovigilance [13], including not only ADR notifications, but any drug-related problem, such as quality deviations, drug ineffectiveness, and medication errors. At the same time, ANVISA launched the Sentinel Network project, whose main objective was regulating and monitoring health technologies used in the tertiary and secondary level of health care. Therefore, only teaching hospitals were responsible for reporting irregularities of health technologies to ANVISA, which would evaluate the safety, quality and effectiveness attributes of products available in the market.

In 2005, with the Reporting Pharmacy project, ADR and technical complaint monitoring was extended to the first health care level. However, the desired number of reports has not been obtained, although each notification is of great importance for patient safety in a qualitative point of view. This project is currently being regulated.

In 2009, pharmacovigilance standards were created for MAH of drugs for human use. In this resolution, pharmacovigilance is understood as ‘pharmacovigilance activities relating to the detection, assessment, understanding and prevention of adverse effects or other drug-related problems. Thus, the following adverse effects or other drug-related problems were considered for reporting: Suspected ADRs; Adverse Events due to drug quality deviations; Adverse Events due to the use off-label; Drug interactions; Total or partial therapeutic ineffectiveness; Drug abuse; Potential or actual medication errors [3].

Brazilian pharmacovigilance legislation demanded about three and a half decades to develop strategies for implementing post-marketing surveillance mainly focused on the drug. Currently, with the publication of new legislations focused on patient safety, the patient also starts to be the protagonist of the treatment process.

Furthermore, strategies for drug registration renewal by submitting periodic safety update reports and risk minimization plans were developed, and actions related to post-marketing surveillance were expanded to all spheres involved in the drug life cycle. Also, the new legislation of 2015 allows ANVISA to define deadlines for drug registration renewal, considering the nature of the product and the health risk involved in its use [14] (Table 1).

Nowadays, not only MAH are required to monitor their products, but health care services also started to be responsible for promoting patient safety, since they evaluate all the process of drug use (the need, safety, effectiveness, and adherence). This allows to analyze the profile of drug use, risk factors for the occurrence of ADEs [15], and problems related to ineffectiveness, such as polymorphism [16], drug quality deviations and medication errors [17,18].

The reporting deadlines are important factors for improving drug risk communication. The legislation sets different deadlines for each sector. While Sentinel Hospitals are required to report serious or non-serious ADEs directly to ANVISA, MAH must report only serious ADEs within 7 or 15 days [3]. Non-serious ADEs will be reported only in the Periodic Safety Update Report during drug registration renewal.

To improve risk communication, the CVS-SP defined that adverse events that involve death must be reported, even when not confirmed by health care professionals [19]. Besides, MAH set in the State of Sao Paulo must report non-serious adverse events to the CVS-SP within 90 calendar days after knowledge of the case, possibly contributing to generate a rapid safety signal for a product.

Moreover, manufacturers do not have access to pharmacovigilance reports concerning their products or to ANVISA's assessment about these reports, since they are sent directly to ANVISA through the NOTIVISA system. It is important to provide this feedback to MAH, since it allows manufacturers to improve the quality and safety of their products. This process is currently ongoing, as the access of MAH to reports involving their products is planned for the version 2.0 of NOTIVISA, which is under construction [20].

Pharmacovigilance actions are conducted in a few services, such as Sentinel Hospitals, Notifying Pharmacies, and some centers and regions of Brazil linked to universities and teaching hospitals in the following states: Bahia, Ceará (Northeast region); Brásilia, Mato Grosso do Sul (Midwest region); Parana, Santa Catarina (South region); Rio de Janeiro Sao Paulo, Minas Gerais (Southeast region) [9,10]. Eighteen Brazilian states, especially in the North region, do not have pharmacovigilance services. The lack of centers in all regions leads to an unequal pharmacovigilance in Brazil, underreporting, and, consequently, failure in detecting signals of new ADEs [21].

Although pharmacovigilance in Brazil is strong in its legislation, other domains are not well structured, which contributes to the disparity of actions in different Brazilian states [22]. Thus, it is necessary to develop new requirements, such as transparency, accountability, information technology, among others, in order to minimize underreporting and promote equity of actions among the different Brazilian regions [22].

Another highlight is that RDC (resolution) 04/2009 [3] and Ordinance CVS-SP 05/2010 [19] only include the technical complaint reporting if an adverse event occurs due to drug quality deviations. Currently, technical complaints, important indicators of drug quality, are mostly reported by Sentinel Hospitals.

In Brazil, reporting events related to veterinary medicines, which are registered by the Ministry of Agriculture, Livestock and Supply (MAPA), that regulates drug registration and renewal, is not compulsory. Veterinary medicines also need a pharmacovigilance system to report ADEs in animals or ADEs observed by humans during drug handling and administration.

A trend for supervising Brazilian drugs would be the harmonization with the European Union, by adding a symbol of an inverted black triangle to the leaflet of new drugs with the following description: “This drug is subject to further monitoring”. As drugs approved for less than five years must have their risk-benefit ratio assessed more frequently, this Brazilian legislation could be harmonized with the European legislation, alerting health care professionals and patients about the exposure to this drug and contributing to drug safety.

Conclusion

The advancement of pharmacovigilance regulation is recent in Brazil. Regulatory advancements equivalent to international practices have been observed only after the publication of the National Drug Policy (1998), the foundation of ANVISA, and the creation of the CNM (2001).

However, the lack of decentralization of pharmacovigilance centers or services in all Brazilian states leads to underreporting and failure in signal detection, especially of non-serious ADE reports for health care.
products and services. There is a lack of regulations for biosimilars and veterinary medicines and of agility in reporting non-serious risks to manufacturers and health care services.

It is necessary to encourage and to develop strategies for technical complaint and quality deviation reporting, in order to improve and control post-marketing drug quality. Also, there is a need for decentralization, leading to a higher equity between Brazilian regions in regards to risk communication related to the use of drugs.

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