



Harmonization of Pharmacovigilance Regulation in Brazil: Opportunities to Improve Risk Communication

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ABSTRACT

Brazilian pharmacovigilance regulations involve 3 spheres: health services, Marketing Authorization Holders (MAHs), and sanitary agency. Drug tolerability began to be effectively assessed in Brazil after the founding of the National Agency of Sanitary Surveillance, which developed the Sentinel Network Project. The objective of the Sentinel Network Project is to increase the adverse drug reaction (ADR) reporting rate by health care professionals in the hospital setting. Pharmacovigilance practices became mandatory for MAHs, and patient tolerability issues were considered in drug policy in Brazil only as recently as 2000. However, despite recent events, the regulatory advancements in pharmacovigilance in Brazil are only equivalent to international practices (ie, those of the European Union). The pharmacovigilance system in the European Union integrates the national authorities, the European Commission, and the European Medicines Agency, which is responsible for the scientific evaluation, supervision, and safety monitoring of medicines for human and veterinary use in the European Union. Furthermore, ADR patient reporting is included in the new EU pharmacovigilance regulations. Numerous possible ways are available to improve the Brazilian pharmacovigilance system, mainly through regulations of biosimilar, nanotechnology, and veterinary medicines or by training health care professionals and patients to report nonserious cases and quality deviations. It is necessary to encourage and develop strategies for decentralizing pharmacovigilance actions in the whole country, as is

common practice in several EU countries. Motivating and considering ADR reports by patients and improving feedback and audit practices in health care services and MAHs are also necessary measures. With the inclusion of Brazil as a member of the International Conference of Harmonization, significant changes in pharmacovigilance regulation are expected; these updates, which will consider international standards, will improve signal detection and risk communication. (*Clin Ther.* 2019;41:598–603) © 2019 Elsevier Inc. All rights reserved.

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According to the World Health Organization (WHO), pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) or any other possible drug-related problems.¹ Pharmacovigilance usually deals with the postmarketing surveillance of drugs in real-world clinical practice; however, recent legislation requires that Marketing Authorization Holders (MAHs) include a product tolerability assessment during clinical trials to consider all aspects of drug tolerability.²

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The tradition of pharmacovigilance in Latin America is relatively recent because most countries initiated postmarketing drug surveillance systems in the 1990s.³ Despite the remarkable changes among regulatory requirements in the last couple of decades, several disparities still remain among Latin American countries.⁴ When compared with developed countries, legislation related to drug tolerability in many developing nations is depicted as lax and weak.⁵

Despite Brazilian investments in the pharmacovigilance processes, which generated significant improvements in patient health through a number of mechanisms (transparency, accountability, policy, law, and regulations),⁶ several concerns remain, particularly those that impair effective risk communication and signal detection, such as a lack of awareness or incentive to report patient effects, the failure of programs aimed to improve reporting rates by pharmacists in primary health care, the absence of National Agency of Sanitary Surveillance (ANVISA) feedback related to regulatory measures arising from ADR reports, the complexity and instability of ANVISA's electronic form for reporting ADRs, and underreporting.⁷⁻⁹

De Carvalho et al¹⁰ reviewed the Brazilian pharmacovigilance regulations published from 1976 to 2015 and observed that the legislation covered 3 spheres: MAHs, ANVISA, and health services. They noticed that, although drug surveillance policies were initiated in 1970, they were considered unsuccessful for the implementation of pharmacovigilance. The state health surveillance centers also had an important role in initiating pharmacovigilance activity; however, the systematization of pharmacovigilance in Brazil truly began when the Sentinel Hospital Network was initiated.¹¹ The objective of the project was to encourage health care professionals who worked at the registered institutions to report ADRs. These reports were sent to ANVISA, which analyzed the information and regulated the pharmaceutical market.

Furthermore, the significant evolution in Brazilian regulations has obliged MAHs to follow the ADRs related to their products and stipulated deadlines for notifications.¹² With the advent of the new legislation,¹³ there was a new focus on surveillance actions on patient tolerability instead of focusing only on the drug. This paradigm break from looking only at the drug was made through the establishment of safety nuclei profiles and establishment of clinical

protocols, such as tolerability in the process of use of the drugs.¹⁰

Recently, there have been no significant changes in the Brazilian political landscape; biological, nanotechnology, and veterinary medicines continue with legislative gaps. Furthermore, the centralization of actions at ANVISA is still present, and the inclusion of patients in incident reports is not encouraged. Nevertheless, when we take into account the minimum pharmacovigilance requirements proposed by the WHO,¹⁴ the size of the Brazilian team for pharmacovigilance activities at the federal level meets the requirements; however, the requirements to monitor ADRs properly are broader in a decentralized health care system and in a country with continental dimensions, such as Brazil.¹⁵

Regarding the notification, the Brazilian system of drug pharmacovigilance, called the National Pharmacovigilance System, is characterized as a passive surveillance system in which spontaneous reporting is the main method of monitoring ADRs.¹⁵ It is a structure not only for analyzing ADRs but also for promoting interactions among different regulated spheres (users, health care professionals, and drug holders) and guiding pharmacovigilance activities by the Brazilian authorities. However, no legal instrument has established a pharmacovigilance advisory committee to provide technical advice to the National Pharmacovigilance System.¹⁵

In response to increased drug user participation in spontaneous ADR reporting, the Notifying Pharmacies Program was developed in partnership with the Sanitary Surveillance and Regional Pharmacy Councils of each state. However, the expected result was not observed and, currently, the program is being restructured; a lack of patient awareness about the reporting systems, insufficient knowledge regarding the problems that should be reported and how to fill out the information in the forms, negative experiences, the absence of feedback,⁷ and inadequate supervision of the sanitary agency were the main limitations that impaired the project.

Although the national ADR reporting system is available for the population to notify the authorities, there are no other incentives to incorporate users into the drug surveillance system. Inclusion of the patient as an active participant in this process contributes to the detection of new signs,¹⁶ and there is scientific evidence of the unique value of the patient's

observations¹⁷; thus, the current methods used in pharmacovigilance need to optimize the use of the information reported from patients to improve risk communication.¹⁸

In the European Union, one approach to improve the inclusion of patients in reporting systems is nonprofit organizations that represent the interests and needs of patients, their families, and caregivers.¹⁹ These institutions have an important role in raising awareness and motivating the patient to talk with their physicians or pharmacists about the occurrence of ADRs and the strategies to report such ADRs to pharmacovigilance systems.²⁰

Concerning pharmacogovernance (ie, government structures and regulations aimed at patient tolerability), the main path being pursued in Brazil is strengthening pharmacovigilance and the ability to monitor and enforce regulatory compliance.²¹ In this context, Moscou et al⁶ investigated whether the governance of ANVISA and support from the international community are sufficient to ensure postmarketing drug tolerability across Brazil.⁶ The authors observed that Brazil's pharmacogovernance was strongest in the domain of policy and law but that gaps in other domains adversely affected postmarketing drug tolerability and led to regional disparities in pharmacovigilance between highly resourced and underresourced Brazilian states.⁶ These shortcomings suggest that signal generation and risk communication can be impeded in Brazil.⁶

PERSPECTIVES

Despite the identified gaps, significant changes in Brazilian pharmacovigilance policies are expected in the future because, in December 2015, ANVISA was accepted as an observer at the International Conference of Harmonization²² and became a regular member in November 2016. Becoming an integral member signals Brazil's commitment to quality, tolerability, and efficacy standards at the international level. In addition, to be a signatory, it is necessary to implement 5 International Conference of Harmonization level II guides by 2021.²³

According to the data presented by ANVISA's Directorate of Health Regulation, the first guide (E2A: management of clinical safety data: definitions and standards) has already been implemented, and the remainder must be completed by December 2021, namely the following: (1) data elements for reporting

individual security cases (E2B); (2) postapproval security data management: definitions and standards for issued reports (E2D); (3) common technical documents for the registration of medicinal products for human use (M4); and (4) Medical Dictionary for Regulatory Activities: terms directly related to pharmacovigilance, with descriptions of adverse events (M1).²³

In addition, the need to harmonize the Brazilian pharmacovigilance standards with international standards has prompted ANVISA to publish public consultation No. 551 of September 3, 2018,²⁴ which deals with good pharmacovigilance practices for holders of medicinal products for human use, and Public Consultation No. 552,²⁵ which concerns the periodic benefit-risk assessment report to be submitted to ANVISA by the holders.

Therefore, communication on drug tolerability and the sanitary risk of drugs will be expanded by ANVISA. Major changes include the training of human resources, continuous improvement programs (self-inspection by companies and third-party audits), document management, and changes in risk communications (including a maximum of 15 calendar days for serious adverse events and serious or unexpected ADRs that occur in the national territory).

Furthermore, MAHs should present a version of a risk management plan in the drug registration process and update that plan when new information about drug tolerability and use is obtained, including information about individuals who were not included in preapproval-phase studies. The update must be performed in specific situations, such as the following: (1) when significant changes in the registry affect the tolerability of the product; (2) when an unexpected damage is identified; or (3) when requested by the competent health authority. Risk minimization plans are an important strategy in public health for managing new risks, monitoring known risks, and, especially, promoting the proper use of medication.²⁶

In relation to nanotechnological products, an ordinance was passed on August 20, 2014,²⁷ that established the ANVISA Internal Committee on Nanotechnology, which, among other functions, is responsible for elaborating the rule that obliges the proponent of the registration to inform users about natural nanotechnological products and the processes

subject to health surveillance. This committee is also responsible for monitoring the elaboration of specific standards or guides for the evaluation of tolerability, monitoring, and control of products, in addition to monitoring the evolution of regulatory policies at the international level.

In addition, the Brazilian parliament is currently analyzing 2 bills, one for the labeling of products that make use of nanotechnology²⁸ and the other for the creation of a national nanotechnology policy,²⁹ which requires knowledge of issues related to nanotechnology safety profiles and a coordinated approach to addressing these issues.

Therefore, considering the lack of scientific evidence on the risk of nanotechnology, regulations should be based on the precautionary principle, and risk assessment should be performed on a case-by-case basis, following the models implemented by the US Food and Drug Administration and the European Medicines Agency.³⁰ The population and health care professionals should be informed when a new drug is registered, and new use should be monitored so that new results can support the regulatory decision in the risk-benefit assessment.³⁰ Moreover, this scenario meets the need for international cooperation and harmonization, as well as the development of regulatory approaches and effective governance.

COMPARISON OF PHARMACOVIGILANCE IN EUROPEAN UNION

In the European Union, an ADR was redefined in December 2010 by Directive 2010/84/EU; this new definition of *adverse reaction* covers noxious and unintended effects that result not only from the authorized medicines at normal doses but also from medication errors and uses outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product.¹⁹ On the other hand, Brazil adopted the following WHO definition: “An adverse drug reaction (ADR) is a response to a drug that is noxious and unintended, and which occurs at doses usually used in man.”

Legislation in Europe is as detailed for the pharmacovigilance of biologics as medicinal products³¹ as for advanced therapy medicinal products.³² The pharmacovigilance legislation for veterinary medicinal products are reported in The Rules Governing Medicinal Products in the EU: Guidelines on

Pharmacovigilance for Medicinal Products for Veterinary Use.³³ At the international level, the Veterinary International Conference on Harmonization provides guidance on pharmacovigilance.³⁴

A significant effort is being undertaken at the European and international levels so that regulatory science continues to evolve in parallel with advances in our understanding of nanotechnology to ensure preparedness for the future challenges of next-generation nanomedicines as well as the optimization of the requirements for abridged (follow-on) medicinal products.³⁵

SUMMARY

There are still shortcomings in the Brazilian regulation of biosimilar, nanotechnology, and veterinary products and in notifications of quality deviations of drugs and nonserious events. As the system of pharmacovigilance of ANVISA is implemented today (centralized system), it impairs risk communication regarding the use of drugs in different regions of the country, as well as adherence to the deadlines for reporting ADRs. Therefore, efforts are necessary to encourage decentralization of drug surveillance activities to consider the particularities of each Brazilian state. Consequently, it might provide feedback and opportunities to enhance pharmacovigilance training for health care professionals and patients.

European legislation has made significant progress when compared with the Brazilian challenges. Decentralized pharmacovigilance systems have been used for several years in multiple European countries, including Portugal, Spain, France, Italy, and the Netherlands. Pharmacovigilance centers are normally integrated in universities or clinical centers and can provide valuable contributions to the national pharmacovigilance system. These centers represent the proximity of the pharmacovigilance system with health care professionals and patients. Through their technical and scientific capacities, they can contribute to the development of pharmacovigilance activities, preparation of pharmacoepidemiologic studies, and training health care professionals, among other activities. These pharmacovigilance centers could participate in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance,³⁶ which is a network coordinated by the European Medicines Agency with research interests in the

tolerability, benefits, and risks of medicines as well as disease epidemiology and drug use.

Finally, ANVISA should address strategies to increase ADR reporting by drug users to improve risk communication and signal detection in Brazil because the role of patient reporting of ADRs has been recognized in the new EU regulation. However, the patient forms should be changed to improve adherence to the system.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinthera.2019.01.013>.

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