Chapter 21
Pharmacovigilance for Herbal Medicines in Brazil

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21.1 Introduction

Brazil covers 8.5 million km^2 and occupies almost half of South America, encompassing several climatic zones that provide great ecological variations and forming distinct biogeographic zones or biomes. The variety of its biomes (Amazon Rainforest, Pantanal, Cerrado, Caatinga, Pampas, and Atlantic Forest) reflects the enormous wealth of Brazilian flora and fauna, leading Brazil to harbor the greatest biodiversity on the planet. This abundant variety of life—translated into more than 20% of the total number of species on Earth—elevates Brazil to the position of the main nation among the 17 countries with the greatest biodiversity [1].

In addition to this genetic collection, Brazil has a rich cultural and ethnic diversity that has resulted in a considerable accumulation of traditional knowledge and technologies, transmitted from generation to generation, among which stands out the vast knowledge collection on the management and use of medicinal plants [2].

Since 2006, the guarantee of safe access and the rational use of medicinal plants and herbal medicinal products (HMPs) in Brazil have been subject of public policies (National Policy for Medicinal Plants and Herbal Medicinal Products and the National Policy for Integrative and Complementary Practices in *Sistema Único de Saúde* (SUS), which guiding principles are the expansion of therapeutic options and improvement of health care for the Brazilian public health system (*Sistema Único de Saúde—SUS*) users [2, 3]. According to 2017 data, Herbal Medicine Services

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were offered in 1108 municipalities and, in the same year, 12 types of herbal medicines that are listed on the National List of Essential Medicines (*Relação Nacional de Medicamentos Essenciais—RENAME*) were freely distributed to the population, representing 2,183,098 pharmaceutical units (where one unit is one bottle, or one blister pack of tablets) of herbal medicines dispensed [4, 5].

The minimum quality requirements for medicinal plants, among other specifications, are described along 83 monographs in the sixth edition of the Brazilian Pharmacopeia, including 22 monographs for tinctures (herbal preparations), 19 monographs for fluid extracts (herbal preparations), and 25 monographs for oils, fats, and waxes.

The Brazilian Pharmacopeia also includes particular documents related to herbal medicinal products and medicinal plants, such as the *Memento de Fitoterápicos* (MFFB) and the *Formulário de Fitoterápicos* (FFFB). The *Memento de Fitoterápicos* consists of a document for a quick consultation, by prescribing professionals, to guide the prescription of medicinal plants and herbal medicinal products. Monograph contents are based on scientific evidence that may assist the prescriber's therapeutic conduct. The second compendium focuses mainly on compounding practices and dispensing of herbal medicinal products, contributing to Herbal Medicine Services and pharmacies across the country [6, 7].

21.2 Herbal Medicinal Products Regulatory Framework

21.2.1 Marketing Authorization

In Brazil, the medicinal plant is defined as the plant species itself, cultivated or not, used for therapeutic purposes, either in its fresh state after harvest/collection or after a drying process. A fresh medicinal plant (or its parts) can be subjected to stabilization processes, when applicable, and drying, taking the whole, torn, comminuted, or powdered forms, constituting what is called a "herbal drug." The product of an extraction from the fresh medicinal plant or herbal drug, which contains the substances responsible for the therapeutic action, is called a "vegetal derivative" (extract, fixed and volatile oil, wax, exudate, and others) [7].

The herbal drug, being the active ingredient in the formulation, can be marketed in this way (without further processing), as a medicinal tea for use in extemporaneous preparations, or it can be marketed in other pharmaceutical dose forms, such as capsules, for example, which may also contain excipients. When the formulation consists of herbal derivatives, whether associated with excipients or not, it can be administered under different pharmaceutical dose forms [8].

An herbal medicinal product is defined as the product obtained from active vegetal raw material (medicinal plant, herbal drug, or herbal derivative), except those that include isolated or highly purified active substances (synthetic, semisynthetic, or natural) or the associations of these with other extracts (herbal or other sources

such as animal), with prophylactic, curative, or palliative purpose. This product category includes the herbal medicines and traditional herbal products (THPs), which can be simple (when the active ingredient comes from a single medicinal plant species) or compound (when the active ingredient comes from more than one medicinal plant species) [9].

The difference between an herbal medicine and a THP is related to the proofs of efficacy and safety when applying for a marketing authorization. The first is based on clinical evidence and is characterized by consistent quality. The second is based on data on safe and effective use (traditional use), demonstrated in technical-scientific documentation, with no known or informed evidence of risk to the user's health. In addition, THPs are designed to be used without a physician's supervision for diagnostic, prescription, or monitoring purposes; cannot refer to diseases, disorders, conditions, or actions considered as serious; cannot contain known hazardous chemical groups in concentrations above safe limits; and should not be administered by injectable and ophthalmic routes [8]. Evidence by traditional use is a form of proof recommended by the World Health Organization (WHO) and seen in major international legislation frameworks for herbal medicinal products, such as those from the European Community, Canada, Australia, Mexico, and Brazil [8, 9].

In Brazil, herbal medicines are subject to "simplified marketing authorization/regular marketing authorization" processes, and THPs are subject to both "simplified marketing authorization/regular marketing authorization" processes and "notification." THPs constitute a new class of medicines created by Brazilian Health Regulatory Agency (Anvisa) in order to make it clear to consumers whether the product they are using has gone through all clinical tests for safety and efficacy proof, or if it has been approved for its effective and safe use on the basis of long-term (traditional use) [8].

Marketing authorization and post-approval changes of herbal medicinal products, as well as notification of THPs, currently follow specific regulations that have been published by Anvisa in 2014 and in line with international regulations. These comprise:

- Resolution-RDC n° 26/2014, which provides for the marketing authorization of herbal medicines and the marketing authorization and notification of THPs [9].
- Resolution-RDC n° 38/2014, which provides for post-approval changes applications for herbal medicines and THPs and other measures [10].

Additional regulatory frameworks of a complementary nature were also published to detail the rules and procedures of external scope with additional guidance to the Resolutions, containing, for example, the "List of herbal medicines for simplified marketing authorization" and "List of THP for simplified marketing authorization"; the Guidance for marketing authorization of Herbal Medicine and marketing authorization and notification of THP and procedures related to Product Change History protocol and the deadline for analyzing post-approval changes applications for herbal medicines and THPs, based on the provisions of Resolution-RDC n° 38/2014 [8, 11, 12].

Beyond specific standards for herbal medicinal products, other general and transversal regulations applicable to different categories of medicines are also applicable here, such as Good Manufacturing Practices; Clinical research for the purpose of proving the safety and efficacy of medicines; Request procedures at Anvisa; List of therapeutic indications exempt from medical prescription; Drug importing rules; Pharmacovigilance guidelines for drug registration holders; Requirements for conducting stability studies; Validation guidelines for analytical methodologies, leaflet and labeling requirements; and advertising rules [8].

Despite the potential for growth in the Brazilian market for herbal medicinal products, and the public policies aimed at expanding its use, the number of licensed herbal medicinal products is considered small when compared to that in other countries, and non-native plant species prevail in the composition of herbal medicinal products in Brazil. There has been a decline in the number of licensed herbal medicinal products over the years. In 2008, 512 herbal medicines were licensed, of which 432 were simple and 80 were combination (multiple ingredient) products. In 2011, there were 382 licensed herbal medicines (357 simple, 25 combination products). In the last survey carried out in 2018, 359 herbal medicines were licensed, 332 as simple products and 27 as combination products. Several factors contributed to this scenario, such as the presence of more restrictive regulatory frameworks, the need for a medical prescription for many herbal medicinal products that do not have this restriction in other countries, and the delay in the analysis of those marketing authorization applications which had to be adapted to the new regulations, among others [13].

21.2.2 Manufacturing and Compounding

The quality of an industrialized herbal medicinal product must be ensured by controlling all stages of its manufacturing, that is, from applying the principles of Good Agricultural Practices (GAP) through Good Manufacturing Practices (GMP) for raw materials, to Good Manufacturing Practices for medicines. Regarding production of plant species for use in herbal medicinal products, GAP must be observed; this provides guidance on the correct cultivation, collection/harvesting, processing, drying, and storage of the medicinal plant. However, the regulation of this activity comes under the Ministry of Agriculture, Livestock and Supply (MAPA) in Brazil, and is not in Anvisa's scope of control, which begins with GMP for Vegetal Active Pharmaceutical Ingredient.

GMP compliance by the manufacturing companies for herbal medicines and THP production is required and a Certificate of Good Manufacturing Practices is the document issued by the Brazilian Health Regulatory Agency stating that the licensed facility complies with the requirements of this regulatory framework [14–16].

Medicine compounding, in general, has its own regulation such as Resolution-RDC n° 67/2007 (Good Practices of Compounding for Magistral and Official

Preparations for Human use in Pharmacies) and Resolution-RDC n° 87/2008 (Amends the Technical Regulation on Good Practices of Compounding in Pharmacies). However, to support the already mentioned public policies outlined for herbal medicinal products, in 2010, the *Farmácia Viva* program was instituted in the SUS through Ordinance n°886/GM/MS. The program aims to produce accessible herbal medicine products to the population and carry out all stages from cultivation, collection, processing, storage of medicinal plants to compounding and the dispensing of Magistral and Official Preparations of medicinal plants and herbal medicinal products. In order to guide the execution of these activities, Resolution-RDC n°18/2013 was published, which provides for the good practices of processing and storage of medicinal plants, preparation and dispensing of Magistral and Official products of medicinal plants and herbal medicinal products in *Farmácias Vivas* within the scope of the SUS [17–20].

21.3 Pharmacovigilance

Pharmacovigilance actions in Brazil are executed by several institutions within the SUS, but are coordinated by the National Monitoring Centre, which is located in the Anvisa's—Brazilian Health Regulatory Agency—Pharmacovigilance Office (*Gerência de Farmacovigilância—GFARM*), according to Ordinance Anvisa's GM/MS n° 696/2001 [21]. Both the Regional Monitoring Centres as well as the Local Health Regulatory Authorities of the 27 Federation Units and the Ministry of Health make up the Brazilian Pharmacovigilance System, together with Anvisa. Each of these institutions has a defined role, with Anvisa coordinating this system and carrying out pharmacovigilance actions at the national level. The Ministry of Health, more specifically, is responsible for pharmacovigilance of medicines distributed by the SUS, with an emphasis on vaccines.

In 2001, Brazil became the 62nd member of the World Health Organization (WHO) Programme for International Drug Monitoring and, since then, pharmacovigilance and other post-market actions for medicinal products have stood out as important tools for drug sanitary control in the country.

In Brazil, ICSRs can be provided/reported by citizens, all health professionals and marketing authorization holders (MAH). It is only necessary to obtain a login and password to access the electronic system for MAHs and health units. Other reporters can provide ICSRs through the Anvisa website. Although numbers of ICSRs are still far from those received in developed countries, Brazil has seen an increasing number of ICSRs submitted per million inhabitants in recent years. From the implementation of a new management system for spontaneous reporting in December 2018, and following a more effective coordination of the National Pharmacovigilance System by Anvisa, Brazil received 13,461 ICSRs in 2018 and 21,896 ICSRs in 2019.

21.3.1 Work Processes

Data collection for detection of signals of adverse events in Brazil is carried out by passive and active pharmacovigilance methods, such as stimulated reporting and observational studies, among other methods. However, it is in passive pharmacovigilance that the country has advanced significantly in a short period of time. In 2018, the management system for spontaneous reporting—Notivisa® (operative since 2006)—was replaced by VigiFlow®, a system made available by the Uppsala Monitoring Centre (UMC). Locally named VigiMed®, this system supports the collection, processing, and sharing of ICSRs, in order to facilitate effective data analysis. In addition, it uses the Medical Dictionary for Regulatory Activities (MedDRA) Terminology, as well as meets the requirements of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B guideline, regarding the internationally harmonized format and standards for data transmission [22].

ICSRs are received, analyzed, and processed daily by GFARM, with the aim of detecting signals. When a signal is detected, an investigative process is opened to search for more evidence in order to strengthen the signal (or to refute it if other evidence does not support it). Restricted (specialized) consultations are directed to Sentinel Hospitals to verify whether that event has also emerged in any other Sentinel Network unit (*Rede Sentinela*).[1] In addition, bibliographic searches are performed on research platforms, websites of international regulatory authorities are consulted, and searches are conducted using VigiLyze®, a powerful research and analysis tool that provides access to more than 20 million ICSRs held in VigiBase®, the WHO global database of ICSRs, contributed by more than 130 countries. VigiLyze® includes data on allopathic drugs, herbal medicinal products, and biological products, including vaccines [23].

Investigations have an undefined term in which to be completed (days, months, or years), depending on their complexity. Sometimes, it is necessary for the marketing authorization holder to provide documents (e.g., updated Periodic Benefit-Risk Evaluation Report) or even the execution of Good Pharmacovigilance Practices inspections at their facilities. When the investigation is completed, some actions may be triggered, depending on the case in question. These are:

- Safety alert publication on the Anvisa website.
- Publication of a letter to health professionals on the Anvisa website.
- Package leaflet amendment demand issued by Anvisa.
- Adoption of precautionary measures (suspension of import, manufacture, distribution, trade, use, etc.).
- Marketing authorization cancellation [24].

[1] *Rede Sentinela* is a strategy, launched in the middle of 2001, with the purpose of being an active observatory for safety and performance of regularly used health products: medicines, medical devices, sanitizers, cosmetics, blood and its components and so on.

21.3.2 Regulatory Frameworks

Basically, there are three regulatory frameworks that cover most of the legal requirements related to pharmacovigilance in Brazil.

21.3.2.1 Resolution-RDC No. 36/2013

This regulatory instrument institutes actions for patient safety in health services, making it mandatory for each health service to create a Patient Safety Centre that must prepare a Patient Safety Plan. This document should identify risk situations and describe the strategies and actions defined by the health service for risk management aimed at the prevention and mitigation of incidents, from admission to transfer, discharge, or death of the patient in the health service [25].

The Patient Safety Centre must also monitor incidents and adverse events that have occurred, reporting them using the electronic tools provided by Anvisa. Adverse events that result in death must be reported within 72 h of the event (death) occurring.

21.3.2.2 Resolution-RDC No. 406/2020 and Normative Instruction N° 63/2020

Resolution-RDC n° 406/2020 and Normative Instruction n° 63/2020 provide for pharmacovigilance rules applied to drug marketing authorization holders. This regulation defines the scope of pharmacovigilance, establishes the obligation to report adverse events and their respective deadlines to do it, as well as the request to submit the Risk Management Plan/Risk Minimization Plan and the Periodic Benefit-Risk Evaluation Reports to Anvisa [26, 27].

These regulations are the result of updating the previous regulation to meet the requirements of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E2B, E2D and M1. Brazil, through Anvisa, was accepted as an ICH observer in December 2015 and became a regular member in the following year. To remain in this condition, Brazil needs to implement five ICH level II guidelines by November 2021, three of which are related to pharmacovigilance and have already been mentioned.

21.3.2.3 Ordinance GM/MS N° 1660/2009

Through this regulatory framework, the Adverse Event Investigation and Report System (*Sistema de Investigação e Notificação em Vigilância Sanitária—VIGIPOS*) has been established as an integral part of the SUS, with the aim of monitoring,

analyzing, and investigating adverse events and technical complaints related to services and products under health regulation in the post-approval phase. This type of work was previously performed by Anvisa and the Ministry of Health in a very specific way, but in 2009 the opportunity arose to formalize and give greater importance to the post-approval monitoring of these products. Ordinance GM/MS n° 1660/2009 clearly establishes the responsibilities and attributions of each of the institutions belonging to the SUS and defines that Anvisa's electronic system for adverse events reporting will be the reference system [28].

21.3.3 Pharmacovigilance for Herbal Medicinal Products

There are no specific regulatory frameworks nor special attention placed on pharmacovigilance for herbal medicinal products in Brazil. Due to the technological limitations of the previous management system for spontaneous reporting (Notivisa), searching for data and reports related to herbal medicinal products is a difficult and laborious process. It is also important to note that, in the previous system (Notivisa), notification by citizens was difficult, as it was necessary to obtain a password and login, unlike the simplified process today with VigiMed®. Nevertheless, 31 ICSRs involving 18 herbal medicines were found in Notivisa and, more recently, in VigiMed, for the period 2006–2020. The largest number of ICSRs is related to the use of *Senna alexandrina*—senna (1 serious ICSR and 6 non-serious ICSRs), *Ginkgo biloba*—ginkgo (2 serious ICSRs and 2 non-serious ICSRs), *Aesculus hippocastanum*—horse chestnut (1 serious ICSR and 2 non-serious ICSRs), and *Piper methysticum—kava kava* (2 serious ICSRs and 1 non-serious ICSR). All ICSRs came from hospitals.

It is expected that from the use of the new management system for spontaneous reporting—VigiMed®—together with other technological alternatives that Anvisa is developing, it will be possible to increase the number of ICSRs and facilitate data searching. However, if the need for more specific monitoring for a given herbal medicinal product is identified, active pharmacovigilance can be triggered in a partnership with the Ministry of Health or another institution belonging to the Brazilian pharmacovigilance system, as it is the case today with antimalarial and multiresistant tuberculosis drugs.

21.4 Final Considerations

With the emergence of a greater number of technologies every day and the need to expand the population's access to new products more and more quickly, the role played by post-market monitoring becomes essential to ensure that patients have access to and use effective, safe, and good quality medicinal products. In this

scenario, special attention is given to pharmacovigilance, which has evolved substantially in recent decades, especially in relation to the tools that are available for its practice. However, when it comes to herbal medicinal products, Brazil still faces difficulties regarding under-reporting. As in many other countries, the likely under-reporting related to herbal medicines may also be a consequence, at least in part, of the way these products are named, distributed, purchased, and perceived by the user.

Certainly, there is much to be done to make pharmacovigilance of herbal medicinal products more effective in Brazil. Nevertheless, advances such as the increased number of ICSR observed in recent years, the adoption of a more efficient management system for spontaneous reporting, the updating of pharmacovigilance regulatory framework directed to marketing authorization holders and incorporation of ICH Guidelines will serve as the basis for pharmacovigilance actions for certain types of drugs, including herbal medicinal products.

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