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Regulatory issues on pharmacovigilance in Latin American countries

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Pharmacovigilance is responsible for monitoring the safety of medicines in normal clinical use and during clinical trials. Legal requirements for pharmacovigilance in some Latin American countries (Argentina, Brazil, Chile, Paraguay and Uruguay) were reviewed. Disparities in the legal framework among the countries are observed being those for marketing authorization holders one of the most evident. The active rol of the universities and drug information centers for/of pharmacovilance seems to be a positive common point. Legal requirements regarding pharmacovigilance of biosimilar medicines, is still a point to be developed.

Keywords: Drug information services, product surveillance, postmarketing, pharmaceutical industry, public health

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Glossary of terms

ADR	Adverse Drug Reactions
AE	Adverse Event
ANMAT	Administración Nacional de Medicamentos Alimentos y Tecnología Médica- Argentina (National Administration of Drugs, Food and Medical Technology)
ANAMED	Agencia Nacional de Medicamentos-Chile (National Medicines Agency)
ANVISA	National Health Surveillance Agency-Brazil
CEBIOBE	Centro de Evaluación de Biodisponibilidad y Bioequivalencia de Medicamentos-Uruguay (Centre for Evaluation of Bioavailability and Bioequivalence of Medicines)
CENIMEF	Centro Nacional de Información sobre Medicamentos y Farmacovigilancia-Chile (National Drug Information and Pharmacovigilance Center)
CNMM	National Center for Drug Monitoring-Brazil
DNVS	Dirección Nacional de Vigilancia Sanitaria-Paraguay (National Direction of Health Surveillance)
ESAVI	Eventos Adversos Supuestamente Atribuibles a la vacunación e inmunización (Adverse Event reports supposedly caused by vaccination and immunization)
ISP	Instituto de Salud Pública-Chile (Institute of Public Health)
LOMAC	Listado Oficial de Medicamentos Actualmente Comercializados- Argentina (Official List of Actually Marketed Drugs)
MAHs	Marqueting authorization holders
MSN	Ministerio de Salud de la Nacion-Argentina (National Ministry of Health)
MSyAS	Ministerio de Salud y Acción Social- Argentina (Ministry of Health and Social Affairs)
NCP	National Centre for Pharmacovigilance
PR	Peripheral Reporters
SAE	Serious Adverse Event
SINFAV	National Pharmacovigilance System-Brazil
SUADR	Serious and Unexpected Adverse Drug Reaction
SUFV	Sistema Unificado de Farmacovigilancia de la Provincia de Córdoba (Provincial Unified Pharmacovigilance System)
SUS	Unified Health System-Brazil
UdelaR	Universidad de la Republica- Uruguay (University of the Republic)
UFARM	Pharmacovigilance Unit-Brazil
UNC	Universidad Nacional de Córdoba-Argentina (National University of Córdoba)
WHO	World Health Organization

1. Introduction

Pharmacovigilance relates to the activities comprising detection, evaluation, understaning and prevention of adverse drug reactions, as well as other reactions caused by medicinal products.

Pharmacovigilance activities have been ongoing for decades which allow it to grow as a scientific discipline [70]. This development has been driven by an increased recognition of its role to foster the safe use of medicines, and more stringent and detailed regulatory requirements [48,72].

The legal pharmacovigilance requirements are changing. In fact, a revision of the European legislation ensures a more proactive approach to monitoring the safety of using medicinal products, both before and after the marketing. In addition, a new

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conceptual model that calls for the pharmacovigilance processes to be involved earlier in the life cycle of a medicine has been developed [49,68].

Pharmacovigilance is responsible for monitoring the safety of medicines in normal clinical use and during clinical trials. Its main aim is to minimize the related to the use of drugs and to maximize their benefits. According to the regulations of worldwide health agencies, pharmacovigilance units collect adverse events from all over the world that were caused or might have been caused by the use of a specific drug. In this context, the following concepts can be defined [11]:

- *Adverse event (AE):* any adverse medical occurrence in a patient or participant in a clinical trial that is produced by a drug, a medical device or a therapeutic procedure which has no necessary causal relationship with this treatment. An AE could be any unfavorable and unintended sign including abnormal laboratory findings, symptoms or diseases temporally associated with the use of an investigational product, whether or not related with it.
- SAE: any undesirable event in the course and in the context of an investigation into a product or a diagnostic or therapeutic procedure that results in death or life-threatening, that requires hospitalization or prolongation of existing hospitalization occurrence, that results in persistent or significant incapacity or disability, which is a congenital anomaly or birth defect or medically significant according to medical criteria. The foregoing is without the necessary existence of presumed causal link between the application of the product or treatment and the adverse event.
- ADR: is a noxious and unintended response to a medicinal product related to any dose. On the clinical experience, before approval of a new drug product or its new usages, particularly when the therapeutic dose cannot be established, any reaction involving a causal relationship between a medicinal product and an AE as a reasonable possibility, i. e. the relationship cannot be ruled out, should be considered as an ADR.
- SUADR: is the adverse reaction resulting in death, life-threatening, hospitalization or prolongation of existing hospitalization or persistent or significant incapacity or disability, whose nature or severity is not consistent with the product information listed on the investigational product monograph or other documentation.

According to Mammi et al. [56], all noxious and unintended effects may be associated with the use of medicines according to the marketing authorization instructions; uses not complying with the wording marketing authorization such as unauthorized use of medication (off-label use), abuse, misuse, medication errors, overdose and ADR related to occupational exposure.

It is widely accepted that despite all the studies performed before the approval of a new product, the knowledge about its benefits and risks until the drug is marketed and widely used is scarce. This is due to the differences between clinical practice and premarketing testing.

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The limited number of patients used in clinical trials in comparison to clinical practice, the shorter period of time for which pre-marketing studies are carried out and the fact that the studies are limited to only one drug are some of the factors contributing to these differences. For this reason, it is very important to set up pharmacovigilance systems in order to monitor the use of marketed drug products, to verify whether their risk-benefit balance is still favorable and to adopt appropriate regulatory decisions with the aim of protecting public health.

Pharmacovigilance rules are necessary for the protection of public health. It must also be emphasized that pharmacovigilance do not only start after their marketing authorization but is the continuation and termination of the analysis performed on medicines starting from the phase I studies, when the medication is administered for the first time in humans. Then, pharmacovigilance activities should cover the whole life-cycle management of medicinal products for human use in relation to safety.

Many epidemiological methods are used for pharmacovigilance activities [50]. However, spontaneous reporting is still the basic method for ADR detection. A major limitation of spontaneous reporting is underreporting by healthcare professionals. Recent studies showed that underreporting ranged from 90% to 95% [51]. In this context, the implementation of methods to promote reporting among health professionals is an important aspect of pharmacovigilance activities. These include facilitating the access to all the methods of reporting, acknowledging receipt of each report of a suspected ADR, providing feedback to the author of the report in the form of journal articles, bulletins on adverse reactions, or fact sheets, encouraging center staff to participate in scientific meetings or to take courses at undergraduate and graduate levels, collaborating with local pharmacovigilance or medicine committees and professional associations, integrating pharmacovigilance into clinical pharmacy and pharmacology development in the country [73].

Pharmacovigilance systems are imperfect. The Pan American Network on Drug Regulatory Harmonization asserts in the document "Good Pharmacovigilance Practices for the Americas" [73] that pharmacovigilance in Latin America is still in the early stages of development. It suffers from the same shortcomings as it does in developed countries: underreporting, redundant reporting of already known adverse effects, conflicts of interest stemming from prescribers and dispensers' links both to each other and to the pharmaceutical industry, and lack of reporting incentives among health professionals. However, others compound these shortcomings: inequitable, individualistic health systems, high percentages of the population with no access to the health system or medical care, and little direct interaction between patients and health professionals, which encourages the use of herbal home remedies not subject to industrial manufacturing and control processes. Other shortcomings are the availability of combination medicines in irrational doses, whose efficacy has not been demonstrated, the use of medicines for off-label indications, not to mention greater problems, such as the ability to purchase medicines as antibiotics without a prescription and the on-line sale of medicines, etc.

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Besides, the use of herbal products continues to expand rapidly not only in Latin American countries but also across the world and concerns regarding the safety of these products have been raised [69]. Herbal products are often perceived by the population as being without risk and its extensive use is partially explained by a widespread belief that such products are "natural" and thus safe.

There are differencies about pharmacovigilance legislation among Latin American countries. The goal of this article is to provide a regional view regarding pharmacovigilance regulations in some countries of the region. Therefore, regulatory information from Argentina, Brazil, Chile, Uruguay and Paraguay was collected.

2. Pharmacovigilance in Argentina

2.1. Argentine National Pharmacovigilance System

The ANMAT was created in 1992 by National Decree N° 1490/1992 [22].

In September 1993, the National Pharmacovigilance System was founded by MSyAS through Resolution 706/1993 within the framework of ANMAT, which depends on the Secretary of Health Polices and Regulation of the MSyAS [23].

In September 1994, Argentina became a member of the Uppsala Monitoring Centre of WHO and since January 1999, it has had access to the international network called Vigimed. This network is an information and discussion list of AE coordinated by the Uppsala Monitoring Centre.

According to Resolution 706/1993 (article #1) the National Pharmacovigilance System is in charge of collecting, evaluating and organizing the information about drugs' adverse effects after their authorization and during their marketing on the whole [23]. In detail, it is in charge of [7].

- Identifying and assessing the effects of acute and chronic use of drugs in the global population.
- Detecting, evaluating and controlling the lack of efficacy as a result of drug utilization during its marketing.
- Evaluating permanently the marketed medicines, with or without prescription.
- Determining the pharmacoepidemiological profile of the population.
- Implementing administrative measures of regulation and control.

The National Pharmacovigilance System is organized by a NCP dependent on the Pharmacovigilance Department of the ANMAT, and PRs set up in different places of the country.

Inside the ANMAT structure, the Pharmacovigilance Department depends on the Direction of Drug Evaluation.

The National Pharmacovigilance System has a Committee of Honor and a National Commission of Pharmacovigilance (Resolution 706/1993, article #4), both exercise their functions *ad honorem* and have neither executive nor management attributes [23].

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Table 1
Categories of the peripheral reporters of the Argentinian's National Pharmacovigilance System and their characteristics

Category	Characteristics
A	PR in activity. They annually send at least 20 reports or 3 serious reports.
B	PR entering the SFVG. Those who do not meet Category A requirements belongs to this category for 1 year
C	Professional associations or societies who serve as consultants of the Systema
D	PR having no activity in the last year.

The NCP constitutes the Pharmacovigilance Department of the ANMAT, which consists of two services: the Security and Efficacy Service and the Drug Information Service.

The NCP gathers the reports from the PRs and from spontaneous reporters (health professionals) or drug users.

The PRs are nationally distributed in public and private institutions with academic and/or clinical prestige such as the Provincial Ministries of Health, Professional Associations, Public and Private Hospitals, Universities, Health Insurances and Professional Societies. The PRs vary considerably in shape, size, resources and scope of their activities. Same data can be found in other Latin American countries and in other continents [59,79].

The PRs send the notifications collected in their area of influence to the NCP. According to the kind of participation in the System, they are categorized as shown in Table 1 [8].

The functions of NCP and PRs are described in the ANMAT Bulletin 1997, Vol. 5, #5 [7].

2.1.1. A formal subsystem (Province of Córdoba)

The SUFV was created by the Ministry of Health's Resolution 183/2005 of the Province of Córdoba [24]. This corresponds with the necessity of adjusting and coordinating between the provincial and national health policy on pharmacovigilance matter, as well as the municipalities and others public and private institutions.

For the best development of the specific activities concerning pharmacovigilance, sub-commissions were constituted in the SUFV for different tasks highlighting, among others, health team training and imputation of received reports. From reports analysis, provincial data are obtained, and then sent to the National Pharmacovigilance System.

The participation of the Drug Information Centre from the Faculty of Chemical Sciences, (National University of Córdoba), in the SUFV is remarkable. The Centre, conducted by the Pharmacy Department, gathers information about requested ADR as recommended in the document "Good Pharmacovigilance Practices for the Americas" [73].

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2.2. Information dissemination and complementary actions

The dissemination of information is a key activity to maintain the Pharmacovigilance Systems. In Argentina, the National System publishes on its official website bulletins of dispositions, bulletins for professionals, the National Official Bulletin, letters to professional associations, and e-mails and/or notes to the PRs [8].

The ANMAT has implemented a set of actions to support the pharmacovigilance activities. For example, Federal ANMAT (http://federal.anmat.gov.ar/federal.anmat/principal.php) was created to improve the articulation and harmonization of the activities between the provinces and the ANMAT. Federal ANMAT is a strategy for strengthening the capacity of regulation and monitoring areas related to drugs, food and medical devices, by continued articulation at both inter/intra provincial and national levels. Through the virtual platform of Federal ANMAT, the Basic Pharmacovigilance Course is given annually to all the health professionals.

As the years go by, ANMAT has been updating the information contained in the drug labels by including data obtained from pharmacovigilance or other studies in the marketing stage of medicines (ANMAT Dispositions 3855/1998 and 5879/2005) [25,63,74].

The information about marketed drugs in Argentina evolved from a simple list of approved products to a link that allows the access to the authorized and current package leaflet of the product. The LOMAC is an official source in which all actually marketed medicines in Argentina are published.

Since 1999, ANMAT has established a time schedule that is updated progressively, for equivalence study requirements for high sanitary risk drugs (ANMAT Disposition 3185/1999, 2814/2002, 758/2009 and 4788/2012) [26,32,34]. Lists of antiretrovirals, high sanitary risk drugs and immunosuppressors with acceptable results of bioavailability and bioequivalence are accessible through the website http://www.anmat.gov.ar/Medicamentos/Medicamentos.asp.

The ANMAT website (http://www.anmat.gov.ar/principal.asp) has links to access to the LOMAC, the National Drug Traceability System (MSN Resolution 435/2011 and ANMAT Disposition 3683/2011) and the Database of Clinical Pharmacology Studies (ANMAT Disposition 6677/2010 and MSN Resolution 1480/2011) [10,11,39,75].

2.3. Argentine National Pharmacovigilance System reporters

The reporters of the National System are those who report a suspected AE to the System. The National Pharmacovigilance System reporters are the following (ANMAT Disposition 5358/2012) [20]:

- Health team professionals (physicians, pharmacists, nurses, odontologist, etc.) from hospitals, clinics, private consultations, pharmacies, etc.
- Patients and relatives of patients: drug users that send their notification to the System.

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– Pharmaceutical Industry: by ANMAT Dispositions 2438/2000 and 3870/1999 [6,30].

The reports are spontaneous and voluntary. They are ADR reporting forms (known as "yellow cards") and can be sent to ANMAT (NCP) or to any other PRs. They are documents that contain confidential information about the identity of the affected person and also the reporter. ANMAT has available on its website http://www.anmat.gov.ar/farmacovigilancia/Notificar.asp the following reporting forms to improve the access to them:

– AE reporting form
– AE Patient's reporting form
– Medicinal Product Quality Defect reporting form
– Medication Errors reporting form
– ESAVI forms
– AE reporting form for using herbal medicines, vegetal products and/or vegetal drug preparations

The surveillance of medical devices (http://www.anmat.gov.ar/webanmat/farmaco/tecnovigilancia.asp) and Odontovigilance (http://www.anmat.gov.ar/webanmat/farmaco/Odontovigilancia.asp) programs were created in 2010 and 2011, respectively, to collect, evaluate and organize information about AE associated to medical devices in general and the ones for odontological use.

The reporters can send the notification forms in digital or printed format (ANMAT website), via e-mail, on line, postal mail, fax, telephone or personally.

2.4. Intensive Pharmacovigilance

Besides spontaneous notification, in Argentina there are drugs under Intensive Pharmacovigilance. It has to do with obtaining information of suspected AE in a systematic, qualified and complete way. It is characterized by its high sensitivity and reliability [5,40].

Unlike traditional methods, Intensive pharmacovigilance applies only to selected drugs known to cause SAE. In addition, its notification is mandatory.

The following drugs are currently under intensive pharmacovigilance:

– Monitoring Program for outpatients and inpatients treated with clozapine
– Talidomide and Lenalidomide Monitoring Program
– Pharmacovigilance Intensive Pregnancy Prevention Program for women of childbearing age who were prescribed isotretinoin systemically
– Medicinal products containing carisoprodol and misoprostol.

2.5. Pharmacovigilance norms and pharmaceutical industry in Argentina

In Argentina, the ANMAT carried out different actions to engage pharmaceutical industry directly in concrete pharmacovigilance activities of its marketed products. A brief abstract of the contents of the norms are mentioned below:

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ANMAT Regulation 2552/1995 [40]

This norm refers to Intensive Pharmacovigilance and specifies the inclusion of active pharmaceutical ingredients in this program when they have at least one of the following characteristics:

- To have demonstrated efficacy in treatment of pathologies when their use justifies the risks of being exposed to the patient
- To be able to cause serious AE, life-threatening events or to have high impact on quality of life, and when those AEs are more prevalent than other therapeutic alternatives that are less efficient for treating the same pathology.
- When an active pharmaceutical ingredient is launched into market to replace another of the same pharmacological group for an indication because of their AE.

All the drugs with an active pharmaceutical ingredient under Intensive Pharmacovigilance must contain on their labels, brochures and professional information, the following legend: "*Medicine under intensive pharmacovigilance. If undesirable effects, described or not on the label, appears, please report to the National Pharmacovigilance System of ANMAT*".

MAHs with at least one of the active pharmaceutical ingredients under Intensive Pharmacovigilance must be made available all the national or international information about AE related to the active ingredient to ANMAT as long as this situation persists. The labels of all these medicines should be modified in content according to the ANMAT requirements, in terms of scientific knowledge available on the date of inclusion under Intensive Pharmacovigilance.

ANMAT Disposition 3870/1999 [29]

This regulation requests that each drug manufacturer and/or importer laboratory appoints a professional belonging to its staff to mediate between the industry and ANMAT, through the Pharmacovigilance Department, to interchange information about AE of drugs.

ANMAT Regulation 2438/2000 [6]

In this regulation, the bases for expanding the participation of the Pharmaceutical Industry in the National Pharmacovigilance System are described. It specifies who, what and where should be notified, the ways and deadlines, and how to interchange information.

The ANMAT proposes the Pharmaceutical Industry that considers the following aspects:

- To reach a consensus between the Pharmacovigilance Department and the Pharmaceutical Industry about the procedure to collect ADRs by different systems they have been using for AE reports.
- To appoint a pharmacovigilance person as a link between the Laboratory and the Pharmacovigilance Department.

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- To jointly develop epidemiological studies of ADRs between the Pharmacovigilance Department and the Industry.
- The information given to ANMAT in the AE reports would be consider confidential attending to professional secret regulation criteria.

ANMAT Notification 08/2009 [5]

In the Annex I of this notification, the Guidelines of Good Pharmacovigilance Practices adopted by ANMAT for all the actors of the system are described. This document has been developed by the Pharmacovigilance Group of the Pan American Network on Drug Regulatory Harmonization from WHO/PAHO perspective to foster and intensify not only the spontaneous AE reports but also the active pharmacovigilance drug studies in Latin America and Caribbean region.

ANMAT regulation 5358/2012 [19]

This regulation establishes the Good Pharmacovigilance Practices for pharmaceutical industry and it is mandatory for MAHs of medicinal products.

In the first part of said regulation, it states the responsibilities and obligations of MAHs, and the characteristics of the inspections to be carried out by the sanitary authority. The second section is centered on the specifications concerning the Periodic Safety Update Reports for the marketed products. And the third part details all the aspects to take into account for elaborating the Risk Management Plans. There is also a forth part focused on Good Pharmacovigilance Practices in vaccines.

2.6. The Role of Universities in Argentina

According to Resolution 566/2004 issued by the Ministry of Education, Science and Technology, Pharmacovigilance should be included as a basic content in the curriculum for the degree in Pharmacy [38]. At the UNC, pharmacovigilance is included in the courses on Hospital Pharmacy, Community Pharmacy and in the preprofessional practice. In postgraduate courses, the subject is taught in the syllabus of the specialization course on Hospital Pharmacy (Faculty of Chemical Sciences-UNC) and in the Pharmaceutical Residence (Faculty of Pharmacy and Biochemistry-Universidad de Buenos Aires). In 2008, the Faculty of Chemical Sciences (UNC) was incorporated as a PR of the argentine National Pharmacovigilance System.

3. Pharmacovigilance in Brazil

In Brazil, the first efforts to address issues related to adverse reactions occurred in the 1970s. In this period, some laws were published (Act No. 6360 (art. 79) [14]; Decree No. 79,094 (art. 139) [13], which were found to be unsuccessful for the development of the country pharmacovigilance attempts [3].

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However, the tasks of national pharmacovigilance are included in the scope of the SUS. The guidelines of Law 8080/90 [15], known as organic health law, states that one should "promote, prevent and recover health with integrated, care actions and preventive activities as well as provide health surveillance activities". However, the effective implementation of this service at a national level began in 1999 with the founding of the National Health Surveillance Agency (ANVISA), with the mission of protecting and promoting health by ensuring the safety of products and services.

Within its organizational structure, a technical unit called Pharmacovigilance Unit (UFARM), which implements and coordinates the National Pharmacovigilance System (SINFAV) was created as part of the organization of a national health surveillance system, whose aim is the safe use and supervision of medicines [33].

The main step in the consolidation of this science occurred in 2001, when Brazil was inserted as an official member of the Upsala Drug Monitoring Program [3]. In the same year, the Ministry of Health issued Decree No. 696 establishing the National Center for Drug Monitoring (CNMM) [17]. These factors were important to the structuring of the pharmacovigilance system in the country [3].

The CNMN initiated the National Pharmacovigilance System (SINFAV) with the implementation of the Sentinel Network comprised of teaching hospitals that monitor the quality and safety of medicines used in hospital settings, and promotes the rational use of these medicines. These hospitals were selected by their size relative to the number of beds and the number of medical residency programs. Besides pharmacovigilance, surveillance of medical devices, haemovigilance, sanitizing products and nosocomial infection surveillance are covered by the program [3].

In 2013, the RDC No. 36 [16], which establishes the actions to promote patient safety and quality improvement in health services, extrapolating the risk management activities for all national health facilities was published.

This resolution confirms the RDC n° 2 [19] which "establishes the minimum criteria to be followed by health facilities for the management of health technologies used in the delivery of health services in order to ensure their traceability, quality, efficacy, effectiveness and safety "of medical products, including drugs, as well as the National Drug Policy, which aims to" ensure the safety, efficacy and quality of medicines, promoting the rational use and access of the population to those considered essential". In this context, all Brazilian health facilities should manage and monitor the risks associated with the use of medications, sending to ANVISA the reports of medication errors, therapeutic ineffectiveness, adverse drug reaction and deviations in the quality of medicines and other events related to surveillance of medical devices, haemovigilance, immunosurveillance and monitoring of sanitization. This information will help the national regulated sector monitor the pharmaceutical market.

In the process of health regulations, pharmacovigilance is directly involved in the post-drug registration activities according to RDC No. 4 of February 10, 2004 [18], which regulates the standards of pharmacovigilance for MAHs of medicines for human use. Under this legislation, the pharmaceutical companies that registrate new

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drugs should prepare at the time of registration renewal (five years) a periodic safety update reports by product, which should include all adverse event of the drug in question. In this document, there will be an overview of the product's safety, plans to minimize risks and pharmacovigilance.

4. Pharmacovigilance in Chile

In Chile, the concern related to AE began in 1972 when Dr. Naranjo and Dr. Mardones published a paper explaining concepts of pharmacovigilance [64]. After this, the study of AE was the main purpose of a Pharmacovigilance Program developed in the Clinical Hospital of the University of Chile. That program lasted from 1972 to 1986 and enforced the role of the pharmacists in the health care team [78]. The method used in the program was a prospective follow- up of the patients during all the time they were hospitalized [65].

Between 1972 and 1986, more than 3600 patients were followed-up and numerous papers were published. Probably, the most known (and cited) work is the one that developed a simple method to assess the causality of ADRs in a variety of clinical situations, and its systematic application to different cases. The Naranjo algorithm is used to classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, and previous patient experience with the medication [67]. Nowadays, some journals have as a requirement before submitting a report of an adverse drug reaction, the use of the Naranjo ADR probability scale to assess the likelihood that the events were drug-related [9]. That Pharmacovigilance Program was useful to demonstrate that the ADRs were more frequent in polymedicated patients, in females [31], in patients with longer stays, in those with liver cirrhosis [66], renal impairment or cardiac failure [35,36], among others.

From 1986 to 1995, only few jobs related to pharmacovigilance were published, most of them carried out by medicine or pharmacy's students and by some of the health professionals who participated in the Pharmacovigilance Program of the Clinical Hospital.

In 1995, a CENIMEF was created under the supervision of the ISP. Professionals from the Clinical Hospital and others with expertise in the analysis of adverse drug reactions were invited to form the Pharmacovigilance Committee. The pharmacovigilance system adopted by the CENIMEF was one based on the voluntary report of suspected adverse drug events. A formulary was designed, according to the WHO recommendation [80], to record the information needed to assess causality, establish severity and system affected, pharmacotherapy used, evolution and sequelae. This form, initially sent by mail, was widely distributed among health professionals from clinics and hospitals that attended training sessions. The CENIMEF was quickly accepted into the WHO Collaborating Center for International Drug Monitoring once

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the first cases of assessed ADEs in Chile were sent. Chile was the fifth South American country to be accepted by the international organization [42]. Since 1996, the CENIMEF has conducted several workshops and two Latin American courses (1998 and 2002) sponsored by the WHO, to train professionals of health institutions and the pharmaceutical industry [37,44].

Pharmacovigilance is taught for more than 30 years at the University of Chile as part of the syllabus in the Pharmacy Career. Currently, it is included in the courses of Clinical Pharmacology and Clinical Pharmacy that are being conducted for the last year students. In addition, during the 6th year of training, the student may conduct a research related to Pharmacovigilance to obtain his/her degree [55]. In the postgraduate areas, the matter is included in the Masters and Doctorate in Pharmaceutical Sciences programs and in the Doctorate in Pharmacology Program. Also, it is incorporated in the Specialization in Clinical Pharmacy Program and other postgraduate courses.

4.1. Chilean National Pharmacovigilance System

The Chilean Institute of Public Health (ISP) depends on the Ministry of Health; its mission is to contribute to the public health care in the country, being the technical and scientific institution that develops, with quality, functions like reference, monitoring and control [76]. The National Medicines Agency (ANAMED) is a Department in the ISP, among its functions there are the control of pharmaceutical products, cosmetics and medical devices authorized by law, which are manufactured locally or imported to be marketed in the country. ANAMED has to guarantee the quality, safety and efficacy of these products [29,57].

According to the WHO recommendation that the medicines agencies must participate in the surveillance of ADEs of the marketed pharmaceutical products, a Subdepartment of Pharmacovigilance was created in the ANAMED [28].

In the Chilean legislation Pharmacovigilance is defined as a set of activities related to the detection, evaluation, understanding and prevention of adverse effects associated with the use of drugs.

Therefore, this sub-department receives all the notifications of suspected AE, identify, assess and record them into a national database. After that, the reports are sent to the WHO Collaborating Center for International Drug Monitoring. The analysis and assessment of suspected ADR are carried out by health professionals that constitute a Consulting Committee. Also, the sub-department promotes the Pharmacovigilance participating in workshops, conferences, and classes for any institution that require these activities [29,43].

In addition, the sub-department has the responsibility of acting as a Drug Information Center, this involves keeping updated drug information sources related to pharmacology and clinic to provide scientific and technical information as required.

Finally, a responsibility of the sub-department is to collect and provide information related to ADEs for the drafting of bulletins and other publications that report on the work done about Pharmacovigilance.

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Table 2
Legislation that regulates the activities of Pharmacovigilance in Chile

Year	Regulation and number	Matter
1993	Resolution 1093	The ISP creates the CENIMEF that was the first organism responsible for planning, assessing and developing the National Pharmacovigilance Program
2004	Resolution 515 (Ministry of Health)	Establish a Health Reform with a National Drug Policy where is mandatory that: – The notification of security problems in medicines or other pharmaceutical products detected by manufacturers or importers. – The creation in health institutions an area responsible for the training in Pharmacovigilance and the recording and notification of AEs. – The notification of quality failures in the medications and possible AEs present in its use detected by the users.
2010	Supreme Decree 3 (Ministry of Health)	Establish the Regulation of the National Control System of Pharmaceu tical Products for Human Use. According to the Title X, health professionals and holders of medicinal products registered in the country must to notify ALL suspected AEs
2012	Resolution 1540	Creates a Committee of Experts for advising the ISP in matters of Pharmacovigilance.
2012	Resolution 1553	Establish the structure of ANAMED, the functions of the Subdepartment of Pharmacovigilance and its Sections (Pharmacovigilance and Drug Information).
2012	Resolution 381 (Ministry of Health)	A Technical General Rule about the National Pharmacovigilance System of Pharmaceuticals for Human Use (Technical Standard No. 140) is approved. This norm is oriented to strengthen the surveillance on drug safety. Also it establish, in a more specific manner, the responsibilities and functions of those who are taking part in activities of Pharmacovigilance.
2012	Resolution 441	Indicates how to proceed to notify ADEs occurred in clinical trials.
2013	Resolution 108	The instructions for the development of the Periodic Safety Update Reports are approved.

Table 2 shows the legislation that regulates the activities of Pharmacovigilance in Chile [38].

While in Chile activities related to the drug safety and its surveillance have been carried out for many years, the development of Pharmacovigilance seems not to have been enough.

The improvement of regulatory aspects is necessary, but it is also essential to have a greater commitment from pharmaceutical industry and health professionals to participate more actively in Pharmacovigilance activities. The participation in activities to achieve the rational drug use will benefit all drug users in the country.

Table 3 compares Brazilian, Chilean and Argentine legal requirements for the pharmaceutical industry.

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Table 3
Comparative regulatory requirements between Argentina, Chile and Brazil for pharmacovigilance in the pharmaceutical Industry

Regulatory Requirements	Argentina	Chile	Brasil
Qualified person responsible for pharmacovigilance	The appointment of a responsable for pharmacovigilance by the Laboratory as an interlocutor with the health authority is mandatory	The technical director is the responsible for the Pharmacovigilance. Also, the responsible could be an external adviser, not necessarily a pharmacist.	No special requirements
Deadlines for the provision of notices (for Marketing autorization holders)	The AE should be notified according to its severity: SAE: must be notified within 15 calendar days. Those which are life-threatening or that produced deaths: within 7 calendar days. AE: must be notified bimonthly	The AE should be notified according to its severity: SAE: must be notified within 15 calendar days. Other AE: the first 5 working days of the month following.	The AE should be notified according to its severity: SAE: must be notified within 15 calendar days. AE: must be notified within 15 calendar days.
Submission of safety reports	Periodic update safety reports should be sent to the Health Authorities with the following frequency, based on the antiquity of the medicinal porducts in the market: – Report twice a year: products marketed less than 2 years. – Report annually: products marketed between 2 and 5 years. – Report triennial: products marketed for 5 years or more.	Periodic update safety reports should be sent to the Health Authorities with the following frequency, based on the antiquity of the medicinal products in the market: – Report twice a year: products marketed less than 2 years. – Report annually: products marketed between 2 and 5 years. – Report each 5 years (maximum): products marketed for 5 years or more.	– Executive summary: every six months (in the first two years) and annually (within three years). – Periodical Pharmacovigilance Report: in the first and second year of its registration. At the time of renewal, an executive summary referring to pharmacovigilance in the period of five years from the Regular Report should be referred to the registration area of ANVISA.
Search in the scientific literature	It is a specific requirement to be included in the Periodic Update Safety Reports and Risk Managment Program	It is not legally required	It is not legally required
Legal requirements	Pharmacovigilance reports should be sent to ANMAT by e-mail or postal mail, via website or phone. There is a link on the website of ANMAT, with publications, annual reports and generated actions.	The notification should be done in a formulary, specially developed by the ISP. They can be sent by mail, e-mail or fax. Also, an electronic form is available for Hospitals and Institutions.	There is na electronic site of ANVISA (Communication in Pharmacovigilance), where alerts, reports and letters for health professionals are available.

5. Pharmacovigilance in Uruguay: University perspective

5.1. Uruguay history in pharmacovigilance

Although Latin American pharmacovigilance systems have developed considerably since the early 1990s and have continued to strengthen, Uruguay had to go through several changes in order to face this new challenge.

First of all, as pharmacists and in order to be part of the health team, a change in the curricula was a need. The integration of basic, pharmaceutical, biomedical

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and social sciences was required. The new pharmacy curriculum with more patient-oriented disciplines such as Pharmacokinetics, Pharmacotherapy, Therapeutic Drug Monitoring, Bioquivalence and Bioavailability, Public Health, Pharmaceutical Care, Chronopharmacy among others and without losing our scientific identity enabled us to assume our role in the health care team being an important step for the implementation of Good Pharmacy Practice. Currently, Pharmacovigilance is included in the course of Pharmaceutical Care and it is also incorporated in some post graduate courses. In addition to this, most of the areas of the Pharmaceutical Sciences Department started working at the university hospital and this fact contributed in working in concert with the patient and the health system to promote health, to prevent disease and to assess, monitor, initiate and modify medication use. The creation of the Pharmacovigilance Unit at the Ministry of Health in 2006 also served the purpose of making the post-approval surveillance of medicines more robust. This Unit, adopting the Good Pharmacovigilance Practices for the Americas (WHO), works in cooperation with the National Advisory Committee, created the same year, which provides technical assistance and is composed of members of the university (Faculty of Medicine, Faculty of Chemistry), members of the public health system and members from other entities. Since its creation, the Pharmacovigilance Unit has started to promote the creation of peripheral effectors or nodes distributed in different parts of the country in public or private institutions. These effectors, according to their structure and characteristics, contribute to the spontaneous reporting system and to intensive pharmacovigilance.

In 2001, Uruguay was incorporated as a member country of The Uppsala Monitoring Centre in Sweden.

In 2007 and by presidential decree, a priority list of drug products whose bioequivalence had to be assessed was confectioned. In 2009, the Centre for Evaluation of Bioavailability and Bioequivalence of Medicines (CEBIOBE) was created. This is a public centre in charge of the University (Universidad de la República, UdelaR). The CEBIOBE performs bioavailability/bioequivalence and pharmacokinetic studies. It is also a qualified centre to work closely with the Pharmaceutical Industry in all the different phases of drug development. It is in charge of developing the protocols and other documents needed for these studies, the preparation of submission to regulatory authorities, the development and validation of analytical methods, the planning and performance of the clinical phase, dosage of samples, result analysis and final report.

The CEBIOBE also has a Pharmacovigilance Programme not only to report adverse drug reactions (ADRs) that can occur during a bioequivalence study with healthy volunteers but also to study interchangeability in the clinical setting between two different drug products already marketed in the country.

Thereafter, the scenario for a functional pharmacovigilance system was displayed.

5.2. Education creates change

Spontaneous reporting of ADR is an important pharmacovigilance method [27, 47]. However, there is underreporting by members of the health team in primary

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health care and in hospitals [21,54]. Low ADR reporting rates associated with prescription medicines are recognized as an international problem. It is generally accepted that less than 10% of adverse drug reactions are reported [4,81].

In 2011 the first pharmacovigilance course named "Pharmacovigilance in Uruguay: an integrating approach" organized by different Faculties (Chemistry, Medicine, Veterinary and Odontology) was carried out as part of the continuing education programme of UdelaR.

The aim of this course was not only to promote spontaneous ADR reporting to the Pharmacovigilance Unit and to create awareness about pharmacovigilance but also to promote intensive pharmacovigilance activities. So our idea as pharmacists and professors in conjunction with students was to contribute from different disciplines and from CEBIOBE to carry out active pharmacovigilance. Therefore several studies were implemented.

5.3. Implemented pharmacovigilance studies

5.3.1. Herbal products vigilance

It is clear that herbal medicines can have adverse effects, including drug interactions [62]. However, relatively little is known about these adverse effects and few adverse reactions are reported to pharmacovigilance systems [46]. Underreporting is even greater for herbal medicines than for conventional medications. Healthcare professionals are often unaware of their use and they do not know what to report.

Educational initiatives were implemented by our group to augment post-market surveillance for herbal products mainly in high-risk pathologies such as AIDS, renal and reno-pancreatic transplantation, liver pathologies and in the psychiatric population. According to our studies, 30% of these patients consume some herbal products. Some interactions between their use and conventional medications were found [53]. Information leaflets about the different medicinal plants were written and given to physicians in order to facilitate information about possible or potential problems with the concomitant use.

5.3.2. Vigilance of the interchangeability in the clinical setting

The aim of biequivalence studies is to demonstrate interchangeability between similar drug products. Such interchangeability means that both drug products present the similar bioavailabilities (biopharmaceutical equivalence) but this fact does not assure therapeutic equivalence (similar pharmacodynamics between the products). Drug products should be considered therapeutically equivalent only if they are tested in patients. In order to do this, the CEBIOBE has implemented a programme of active pharmacovigilance in the clinical setting between the drug product test (T) and the reference (R) whose bioequivalence or bioinequivalence (in the case of extended-release products compared to conventional-release ones) has been demonstrated before. The same patient receives either the T or the R product and then the products are interchanged. In other words, it is the vigilance of the interchangeability in each

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patient. Therapeutic equivalence will be concluded if pharmacodynamic responses assuring efficacy and safety (incidence of adverse effects) between both products do not differ.

5.3.3. Pharmacovigilance in vulnerable patients

As populations get older, the rate of chronic diseases rises, and hence the number and diversity of drugs used increase so the risk of inappropriate drug use increases as well. As the number of elderly people increases in the world population, and our country does not escape from this reality, the quality and safety of drug prescribing are becoming a global health service problem.

In a pilot study carried out by our group with 78 patients over 65 years old, all of them were polymedicated and the total number of medicines prescribed was 862 with a range of 4–21 per patient and a median of 11.

STOPP (Screening Tool for Older Person's Prescription) and Start (Screening Tool to Alert doctors to Right Treatment) criteria [71] has become a valuable tool to detect inappropriate prescriptions in the elderly and a valuable tool for active pharmacovigilance in this group.

5.3.4. Pharmacovigilance of SADR

Serious adverse drug reactions are a major cause of morbidity and mortality worldwide. Some of them may be predictable, based upon a drug's pharmacodynamic and pharmacokinetic properties. Based on the latter, our group is studying hyperammonemia caused by long term high dose valproic acid therapy [61]. Many ADR, however, appear to be idiosyncratic. Genetic factors may underlie susceptibility to these reactions. Based on this, we are studying cutaneous rash reactions to anticonvulsant drugs [60].

We are aware that a successful pharmacovigilance system requires more than inputs and analysis of drug safety data. It also must generate an output. We think that from the university and working in the university hospital we can contribute to the pharmacovigilance system by training students and other helath professionals and by carrying out different intensive pharmacovigilance activities.

Since the creation of the Pharmacovigillance Unit, the number of peripheral effectors or nodes has been increasing steadily and nowadays there are eighteen peripheral nodes in Uruguay. The number of spontaneous notifications has been increasing year after year as well. There were almost 500 notifications in the year 2012 and the number has doubled in 2013. Our joint effort (health professionals, University, Ministry of health) is already generating outcomes.

6. Pharmacovigilance in Paraguay

In Paraguay, the Law 1119/97 about Health and Other Products defines pharmacovigilance as "the identification and assessment of the effects of acute and chronic

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use of drug therapies in the general population or in subgroups of patients exposed to specific treatments."

It also specifies in Chapter IX, Section 36 that:

- Health professionals have to quickly communicate the toxic, unexpected effects or AE that may be caused by medications, to health authorities or authorized centers.
- MAHs either manufacturers or representatives are also required to report to the health authorities the AE they were aware and which may have been caused by drugs they manufacture, import or market.
- The national health authority shall regulate, implement and coordinate a National Pharmacovigilance System through a National Pharmacovigilance Commission composed of representatives of health and qualified experts.
- The national health authority shall assess the information received and integrate international pharmacovigilance programs when appropriate.
- All health professionals must cooperate in the pharmacovigilance system.
- Data from pharmacovigilance systems will not be conclusive until they are reliably evaluated by the National Health Authority.

Through Resolution SG No. 360, (2001) the National Drug Policy was approved. It establishes the creation of the National Pharmacovigilance System, establishing that National Health Authority will regulate, implement and coordinate it through a National Pharmacovigilance Technical Committee that consists of representatives of health authorities and assigned qualified experts. The national pharmacovigilance system was implemented by Ministerial Resolution No. 95 (2010). Through this resolution the National Pharmacovigilance Commission was formed and the participant institutions and organizations were designated. The DNVS dependent on the Ministry of Public Health and Social Welfare is the coordinating body in terms of pharmacovigilance activities in Paraguay.

In 2011, to promote pharmacovigilance in Paraguay, the DNVS adopted the document about Good Pharmacovigilance Practices for the Americas [73] as a basis for developing a Guideline for Regulations, Procedures and Good Pharmacovigilance Practices.

This guideline provides a model of a "yellow card" to report AE of suspected and/or potential problems related to them, which is still in the approval process. At present, Paraguay is not an active member of The Uppsala Monitoring Centre.

The mentioned dispositions are still conducted in a non-systematized way. The lack of diffusion and scarce of skilled profesionals are believed to be the main causes of non-complience. In an effort to strengthen pharmacovigilance system in Paraguay, the Drug Information Center of the Faculty of Chemistry (UNA) has carried out research projects in the field since 2008, and trained health professionals from public and private institutions in order to promote the culture of reporting AE and to strengthen and support the efforts of the DNVS.

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Pharmacovigilance is taught at the UNA as part of the syllabus for the degree in Pharmacy, and is included in the subject about quality management which is conducted for the last year students. In the postgraduate courses, pharmacovigilance is included in the Specialization in Clinical Pharmacy and Pharmaceutical Care.

Besides, the Doctorate in Pharmaceutical Sciences incorporates in its program several courses of Clinical Pharmacy and Pharmaceutical Care Program.

7. Summary

Pharmacovigilance regulatory requirements in Latin America have undergone major changes in the last decades. However, big disparities among the countries still remain. Some of them have legal requirements approaching those of high health survilleance. Others are still developing, with great demands for improvements in the system implementation. Legal pharmacovigilance requirements for MAHs are one of the issues for disparity between Latin American countries. Brazil, Chile and Argentina are the only countries that have similar legal requirements that complement those porposed by the Good Pharmacovigilance Practices for the Americas [73].

The active rol of the universities and drug information centers in pharmacovigilance seems to be a positive common point highlighting that this activity is not only considered a responsibility of the regulatory bodies but also of the whole health system.

Legal requirements regarding pharmacovigilance of biosimilar medicines, are points to be developed in order to harmonize regulations with those more developed such as European Union pharmacovigilance regulations.

Good cooperation between regulatory authorities, industry, healthcare professionals and academia is necessary to ensure the implementation of the requirements and functioning of the pharmacovigilance systems in the region.

Finally, although it is not the objective of this work, it would be interesting to know if the legal requirements are accompanied by more and better reports.

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