PANDRH Technical Document Nº 5

Pan American Network on Drug Regulatory Harmonization

Working Group on Pharmacovigilance

Good Pharmacovigilance Practices for the Americas

Pan American Health Organization
Regional Office of the World Health Organization

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1. Foreword

The potential toxicity of certain medicines is an issue of particular concern among patients, physicians, prescribers, dispensers, and regulatory authorities, as adverse reactions are a major cause not only of medical consultations but hospital admissions and, occasionally, patient deaths. Moreover, in recent years, many medicines have been withdrawn from the market as a result of an unfavorable benefit/risk ratio not detected when their sale was authorized.

As described in the report of the World Alliance for Patient Safety of the World Health Organization (WHO) (1), some of the main requirements of programs for improving patient safety are quality and the capacity to obtain the most complete information possible on adverse reactions and medication errors, so that these programs become sources of knowledge and serve as the foundation for future preventive action. If appropriate steps are not taken when an adverse reaction to a medicine occurs or when new evidence is obtained in this respect, no lesson is usually learned, the opportunity to make generalizations about the problem is missed, and the capacity to develop broader, more effective and more applicable solutions will not be developed (1). Two key lines of action are therefore essential: a) proper training in clinical and therapeutic pharmacology at all levels to ensure better use of medicines, and b) the creation of a pharmacovigilance system.

Health needs and medicine usage varies widely from country to country. There are many reasons for this, among them economics, ethnicity, culture, the burden of disease, and diet, as well as a country's development level and medicine regulatory system. As a result, decisions concerning safety and efficacy must be considered in the specific context of each country. Thus, monitoring of the safety and efficacy of medicines must be a public health priority.

Pharmacovigilance systems are imperfect. The development of the Pharmacovigilance in Latin America and the Caribbean is still in the early stages of development, suffering 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 such as antibiotics without a prescription and the online sale of medicines, etc.

It is within this context that the issue of pharmacovigilance in the 21st century must be addressed. Hence, there is the importance of ensuring its harmonization in the Americas and promoting the development of guidelines for good pharmacovigilance practices and risk management systems. There must be the creation of active pharmacovigilance programs based on pharmacoepidemiology, since planning activities prior to the approval of medicines will benefit public health in the Region.

PAHO/WHO is interested in developing guidelines for good practices used to facilitate and improve the pharmacovigilance reporting system and, thus, patient safety. At the very least, this process will produce feedback from the conclusions of the data analysis. Ideally, it will also yield recommendations for changes in health procedures and health systems—for example, conducting significant in-depth analyses and using the findings, and learning from reports. Disseminating lessons learned, calls for competencies and various other human and financial resources. The authority receiving the reports must be capable of influencing solutions, as well as disseminating the information and making the pertinent recommendations for change (2).

2. Objectives of the Paper

In preparing this paper, the Pharmacovigilance Group of the Pan American Health Organization's Pan American Network for Drug Regulatory Harmonization (PANDRH) adopted the perspective of PAHO/WHO, which considers pharmacovigilance, an essential component of public health programs (3). Its intention was to facilitate the development of pharmacovigilance systems in the Region of the Americas and improve, strengthen, and promote the adoption of good practices to improve safety for patients and the general population, based on the needs of the Region.

This document offers guidelines for answering two questions:

- What needs to be done to set up a pharmacovigilance system?
- How can an existing pharmacovigilance system be improved?

The recommendations are based on WHO documents designed not only to improve the spontaneous reporting system for adverse events but also to promote active pharmacovigilance studies in Latin America and the Caribbean. Countries can select, adapt, or modify the recommendations in keeping with their needs and their legislation to ensure all stakeholders are included. For reference, this document is accompanied by an application guide. (See Annex 1: Project Evaluation Indicators for Reference Agencies in the Region of the Americas and Guide to their Application.)

2.1. Document Structure

The document is divided into numbered sections. Section 3 contains a brief description of pharmacovigilance in the context of the use of medicines. Section 4 is devoted specifically to good practices in the discipline; it describes how to set up a pharmacovigilance center, from the necessary supplies to basic operations. Section 5 describes good practices for analyzing, managing, and communicating the risks identified by the system. Section 6 describes the functions and responsibilities of the specialized personnel in charge of pharmacovigilance. The subsequent sections contain terminological information, a generic reporting form, and guidelines for the analysis of reports, providing causality algorithms and other useful materials for pharmacovigilance activities.

To facilitate the selection and adaptation of elements in this document, those considered indispensable have been marked with the symbol (!!!), and those considered desirable, (!!).

3. Introduction

Modern medicines have changed the way we treat diseases or alterations in health status. However, despite all their advantages, there is mounting evidence that adverse medicine reactions are a common, though often preventable, cause of disease, disability, and even death. In some countries, adverse medicine reactions are estimated to be between the fourth and sixth leading cause of death (3-5).

The approval of a medicine for sale implies that its efficacy has been demonstrated and that any undesirable effects encountered during premarketing testing were acceptable, *although this does not mean that the benefit/risk ratio is definitive*. Once on the market, the medicine leaves the secure and protected scientific medium of clinical trials behind, becoming a legal product for sale to the public. What most commonly occurs is that when a medicine is put on the market, its short-term efficacy and safety have been tested on only a few carefully selected individuals. The information obtained in clinical trials in the different phases leading to its approval by the health authority is not enough to predict what will happen in daily clinical practice when it comes to rare or slow-to-develop adverse reactions, which are most likely to be detected in the post marketing phase. Sometimes, as few as 500 people have received a medicine before it is put to release on the market, and the number rarely exceeds 5,000. Therefore, it is essential to monitor the safety and efficacy of new therapies that are relatively untested from a medical standpoint once they are sold under real-life conditions.

More information is usually needed on the use of medicines in specific population groups, especially children, pregnant women, and the elderly. For example, it is critical to detect secondary effects that are serious, rare, or occur only in children and to verify the safety and efficacy of a product after a lengthy period of uninterrupted use, especially in combination with other medicines. Experience shows that many adverse effects, interactions with food or other medicines, and risk factors do not come to light until years after a medicine is put on the market.

In order to prevent or reduce the harmful side effects of medicines for patients and thus improve public health, mechanisms for assessing and monitoring the safety of medicines for clinical use are essential. In practice, this means having a well-organized pharmacovigilance system.

3.1. The Concept of Pharmacovigilance

WHO defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.”

Its objectives are:

- To improve patient care and safety with respect to the use of medicines and all medical interventions;
- To improve public health and safety with respect to the use of medicines;
- To detect problems related to the use of medicines and communicate the findings in a timely manner;
- To contribute to assessment of the benefits, harm, efficacy, and risks of medicines to prevent harm and maximize benefits;
- To encourage safe, rational, and more effective use of medicines (including cost-effectiveness);
- To promote understanding, education, and clinical training in pharmacovigilance and effective communication to the public.

A good medicine safety and pharmacovigilance service is a prerequisite for early detection of risks associated with medicines and the prevention of adverse medicine reactions. Moreover, it enables health professionals and patients to attain the best benefit/risk ratio with safe and effective therapies. Pharmacovigilance plays a key role in pharmacotherapy decisions at the personal, regional, national, and international level (5).

Here it is important to define the term "adverse medicine reaction," which, according to WHO, is "a harmful, unintended reaction to a medicine that occurs at doses normally used for prophylaxis, diagnosis, or treatment of disease, or for the modification of a physiological function." This definition implies a causal relationship between the administration of the medicine and the appearance of the reaction. Today, the preferred definition is "an undesirable effect attributable to the administration of...," reserving the original WHO definition for the concept of *adverse event*, which does not necessarily imply a cause-and-effect relationship.

Pharmacovigilance studies the undesirable effects or adverse reactions produced mainly, but not exclusively, by medicines, since its sphere has expanded to include herbal remedies, complementary medicines, blood products and biologicals, vaccines and medical devices, medication errors, inefficacy, and other causes (6). These latter include the use of medicines for off-label purposes where adequate scientific evidence is lacking, the use of substandard medicines, acute and chronic poisoning, medicine abuse and misuse, and medicine interactions with other remedies, chemicals, foods, and beverages. Pharmacovigilance also includes studies of medicine-related mortality.

In recent years, the media—newspapers, television, the Internet—have promoted "medicalization," encouraging the public to use medications for "minor symptoms" or simply to "get healthy." This has led to or increased the incidence of largely preventable adverse reactions that can result in death or disability or at the very least, prolong hospital stays.

Nutrition and diet in a community affect the therapeutic efficacy and safety of medicines. Without proper guidance and health professionals with training in pharmacovigilance, patients may be at higher risk of medication errors or preventable adverse reactions.

In combating the risks from the use of medicines, demands close and effective collaboration among the principal entities involved. Success and future outcomes will depend chiefly on the continued willingness to collaborate. Those in charge must engage in concerted action to anticipate, describe, and meet the demands and expectations of the public, including those of public health administrators, planners, politicians, and health professionals. However, sound integrated mechanisms that would permit collaboration of this type are lacking. The main stumbling block is usually the poor training of professionals, as well as a lack of resources, political backing, and most of all, scientific infrastructure. Understanding and tackling these problems is essential and a prerequisite for the future scientific development of pharmacovigilance (4). Clearly, the countries of Latin America and the Caribbean must be prepared if they are to make progress in the new pharmacovigilance.

The pharmacovigilance model that will be adopted must be well grounded as well as flexible, as it will not always be used in countries with preexisting public health and pharmacovigilance systems, but rather, in countries with weak, deficient programs. The model must stress the sharing of human resources and the dissemination of

knowledge about the benefit/risk ratio, collaboration, effective communication, integration, training, and capacity building.

3.2. Methodology

Various methods are used in pharmacovigilance activities (2):

- A spontaneous reporting system based on the identification of suspected adverse medicine reactions by health professionals in their daily practice and the forwarding of the information to an agency that centralizes it. This is the methodology employed by the participating centers of the WHO Program for International Medicine Monitoring;
- Intensive pharmacovigilance procedures based on a systematic collection of detailed data on all harmful effects in specific population groups that can be assumed medicine-induced. These methods are divided into two major groups:
  - Medicine-centered systems;
  - Patient-centered systems
- Epidemiologic studies, whose purpose is to confirm a hypothesis—that is, to establish causality between the presence of adverse events and the use of a medicine. They may be cohort or case-control studies.

The most widespread of the pharmacovigilance study methods is the spontaneous reporting system, also known as the "yellow card system." Systematic reporting of adverse reactions and their ongoing statistical analysis would make it possible to issue an alert or "signal" about the behavior of medicines in the population of our Region (6). The success or failure of any pharmacovigilance activity depends on the reporting of the suspected adverse reactions.

3.3. Background and International Context

The phocomelia epidemic among newborns in Europe in the 1960s, caused by the use of thalidomide, led several countries to begin monitoring medicines. In 1968, under its Program for International Medicine Monitoring, WHO proposed the creation of an international pharmacovigilance center. Located in Uppsala, Sweden (Uppsala Monitoring Center, or UMC), the center currently has 86 countries as active members, the newest being Kazakhstan and Barbados, which joined in July 2008.

In the Region of the Americas, Latin America and the Caribbean are making major efforts to document adverse events linked with medicines, but this is a relatively recent phenomenon. Since the 1990s, 12 countries have set up pharmacovigilance systems under their regulatory agencies and have been recognized as members of the WHO Center for International Medicine Monitoring. The other countries, while not officially members yet, are in the organization phase of pharmacovigilance (7). They will be considered associate members of the Center until their young regulatory agencies are formally recognized as full-fledged centers for the monitoring of adverse reactions.

A variety of reporting systems are used around the world that differs in their nature, scope, and complexity. A study published in 2002 compared the characteristics of different spontaneous reporting systems by surveying the regulatory agencies of 19 countries participating in the WHO International Medicine Monitoring Program. Thirteen (13) countries returned the survey (Australia, Belgium, Canada, Denmark, France, Germany, Ireland, the Netherlands, New Zealand, South Africa, Spain, the United Kingdom, and the United States). Austria, Finland, Greece, Italy, Portugal, and Sweden did not respond (8).

Some of the characteristics of the reporting systems are described below. Reporting by health professionals is voluntary in all the countries except Spain and France, where it is mandatory. Some nations have a decentralized system: France has 21 regional centers, and Spain 17 autonomous centers, with one coordinating center. Canada and the United Kingdom have a partially decentralized reporting system. The remaining countries have a single regional center. The pharmacovigilance programs in other countries include reporting of adverse reactions to products other than medicines for human use. Thus, veterinary medicines are included in Denmark, and medical devices in the United States. Moreover, some countries have monitoring systems that record adverse effects attributable to vaccines that are independent of the program for adverse medicine reactions. Other nations have recently developed systems to monitor specific products such as antiretroviral, antimalarial, and anthelmintic

medicines. The pharmacovigilance programs, based on cohort studies, to monitor antiretrovirals in developing countries are a good example of active pharmacovigilance (9) that should be imitated and expanded.

3.4. General Information on Reporting Systems

The most important objective of pharmacovigilance is the identification of adverse events connected with medicines. Clinical observation and the reporting of suspected adverse reactions are usually the fastest and most effective methods for triggering "alerts" (or signals) or causality hypotheses, as well as for designing specific studies on active pharmacovigilance to determine the safety profile of medicines used by the general public or specific subgroups.

For any pharmacovigilance system to be effective, all health professionals in contact with patients who use medications must be involved in reporting. It should be recalled that all of the information should be centralized in a specialized agency and validated by the health authority for timely dissemination to the community.

The object is to obtain greater safety in the use of medicines through rapid detection of serious adverse reactions, especially with newer products, determining the rate at which adverse effects occur, any predisposing factors, causal relationships, and medicine interactions and studying special population groups (children, pregnant women, people with kidney or liver failure, AIDS patients, etc.). It will also be accomplished by developing training and information programs for health workers to encourage their active participation.

The main purpose of any reporting system is to learn from experience. Reporting for the sake of reporting does not improve safety; thus the response to reports leads to positive change. The important thing is for a pharmacovigilance system to trigger a visible useful response, not only to justify the resources spent on reporting but to encourage individuals and institutions to report. These procedures promote different ways of learning and improving safety, by triggering alerts, disseminating information on experiences, analyzing risk trends, and improving system operations.

Pharmacovigilance systems in Latin America and the Caribbean will have to be more proactive than reactive in the face of alerts and/or the recall of medicines from the market, and they must develop cooperation mechanisms to develop capacities and increase the possibilities of operating as a Latin American pharmacovigilance network (10). However, any effort will be in vain if it is not accompanied by extensive action to buttress the clinical and therapeutic rationale for using a medicine.

4. Good Pharmacovigilance Practices

4.1. General Principles

Effective pharmacovigilance requires a set of rules, operating procedures, and practices that must be followed to ensure the quality and integrity of the data produced in specific types of research or studies. It relies on obtaining complete data from spontaneous reports of adverse events, also known as case reporting.

Objective

Good pharmacovigilance practices are designed to guarantee:

- The veracity of the data collected, for proper assessment of the risks associated with the medicines;
- Confidentiality with respect to the identity of people who have experienced or reported adverse reactions;
- The use of standard criteria to evaluate reports and issue signals or alerts.

Since effective pharmacovigilance depends on input from many people with very different training, to create a coherent pharmacovigilance system it is important to develop guidelines containing standard operating procedures (see section 4.3.2.2 procedures) that describe the practical details of the information flow (11). These guidelines should clearly state and standardize the information on:

- What constitutes a reportable adverse event;
- Who should report a suspected medicine-related problem;
- The availability of reporting forms or yellow cards and how to fill them out;
- Procedures for submitting or compiling reports;
- Routines for assessing, monitoring, and processing case reports in pharmacovigilance centers;
- Procedures for analyzing aggregate data and potential courses of action.
- Good communication practices.
- Indicators that will be used to measure progress in the monitoring system.

In order to follow these good pharmacovigilance practices:

- Reports of suspected adverse reactions or problems related to medicines must be recorded, adhering to the principle of veracity in the data provided;
- All reports where the severity of the suspected adverse reaction warrants it or where there no precedent of such a reaction (that is, when there are indications that it is novel) must be rigorously documented;
- The information on any suspected adverse reaction or other medicine-related problem must be verifiable, corroborating its authenticity and consistency with the original documents whenever possible;
- The confidentiality of information that could identify the people involved must be safeguarded, respecting their privacy and the rules of confidentiality;
- Information must be handled in a way that maintains the reliability of the data, using words that are the same or as similar as possible to those used by the notifier:
- The deadlines established for communicating serious suspected adverse reactions should be scrupulously respected to give them the highest priority;
- Any individual involved in the assessment of an adverse reaction must be qualified for the task based on his or her education, training, and experience;
- All information that has not yet been validated should be viewed with caution;
- All information on adverse reactions must be recorded, processed, and stored in a manner that enables it to be communicated, verified, and accurately interpreted;
- Before communicating an adverse reaction to the scientific community, the National Pharmacovigilance Program must be notified;
- Systems and procedures must be established to ensure quality in the generation, handling, and processing of information on adverse reactions;
- The information collected in the reports on suspected adverse reactions shall in no case be used to make value judgments about the medical intervention.

4.2. Setting up National Pharmacovigilance Systems and Centers

Setting up a reporting system for adverse reactions requires certain capacities, some of them simple and others more complex. It is essential to be clear about: objectives; who should be responsible for reporting; how to obtain the reports; mechanisms for receiving them and handling the data; expert analysis; the capacity to respond to reports; the methodology for classifying reported events; the capacity to disseminate findings; the technical infrastructure; and data security.

Setting up a pharmacovigilance center requires the following:

- *Publicity:* It should be understood that when a national center begins operations, a great deal of effort will be necessary, especially in the area of publicity, before a significant proportion of professionals will participate;
- *Administrative continuity*: When a center is part of a larger organization—for example, a toxicology monitoring unit, a clinical pharmacology department, or a hospital pharmacy—there should be administrative

continuity, which can be ensured by giving a professional—for example, a pharmacist or doctor—the main responsibility for pharmacovigilance;

- *Government resources:* Whatever its place in the organizational structure, pharmacovigilance should be closely allied with medicine regulation. Government resources are needed for national coordination;
- *Collaboration, coordination, communication, and public relations:* In order to ensure coherent development and prevent the overlapping of competencies and unnecessary duplication of efforts, good collaboration, coordination, communication, and public relations are necessary.

4.2.1. Basic Activities for Setting up a Pharmacovigilance Center

Setting up a new pharmacovigilance center is relatively easy. However, developing a pharmacovigilance system from the initial stage to the point where it is an effective, established organization is a process requiring time, vision, dedication, competence, and continuity (12).

A plan for a pharmacovigilance system should be drafted (!!!) that includes the following:

- Contacting the health authorities and local, regional, or national institutions and groups working in the fields of clinical medicine, pharmacology, and toxicology, stressing the importance of the project and its purposes;
- Setting up the center: main office, technical staff, other locales, telephones, word processors, database management capacity, bibliography, etc.
- Designing a reporting form (see example in Annex II) and beginning the data collection process by distributing the form to hospitals, clinics, family doctors in primary health care, and pharmacies;
- Preparing printed materials to inform health professionals about the definitions, objectives, and methods of the pharmacovigilance system;
- Training pharmacovigilance personnel in the following tasks:
  - Collecting and verifying data;
  - Interpreting and coding descriptions of adverse reactions;
  - Coding medicines;
  - Assessing causal relationships;
  - Detecting signals;
  - Managing risks;
- Installing a database—that is, a data storage and retrieval system;
- Holding meetings in hospitals, universities, and professional associations to inform professionals about the principles and demands of pharmacovigilance and the importance of reporting;
- Stressing the importance of reporting adverse medicine reactions in medical journals and other specialized publications.

4.2.1.1. Community Involvement in Pharmacovigilance Systems

Patients can actively participate in developing knowledge about medicine safety profiles as the notifiers of adverse events and important co-protagonists in reporting to the system. It is a good idea to distinguish the reports that come from patients, respecting the principles of confidentiality;

The community should be properly informed about any medicine safety problems in a timely manner.

4.2.2. Financial Resources

In order to guarantee the continuity of its work, a pharmacovigilance center should have a *regular source of basic funding (!!!).* The principal costs involved are for staff, training, communication, computer hardware and software, and the printing of promotional literature and reporting forms.

The resources can be obtained from registration fees or by imposing a special compulsory pharmacovigilance fee (12). Both can be included in the budget of the medicine regulatory authority.

In addition to basic resources, the center can obtain additional funds (!!) from other entities with an interest in pharmacovigilance. The following institutions are examples of those that can be contacted:

- Government departments concerned with medicine safety;
- Health insurance companies and funds
- University departments
- Professional associations

Due to the significant implications of adverse reactions for public health and trade, the continuity of pharmacovigilance funding must be guaranteed. Thus, efforts must be made to ensure that the people responsible for pharmacovigilance are not exposed to the potential influence of pressure groups or the fallout from political or economic change.

There is the estimation of pharmacovigilance funding needs, bearing in mind that the figure will be based on the reporting rate and the size of the population, and other variables (12) related to the cost of collecting quantitative and qualitative data, careful assessment, and distribution of the respective information.

4.2.3. Location

It is essential to have a specific physical space (!!!) with the respective personnel, equipment, and supplies. The most suitable locale for a new pharmacovigilance center will depend on the structure and development of the country's national health system and other local considerations.

A government entity (whether the health authority or a national medicine regulatory agency) can be a good place for a pharmacovigilance center. Nevertheless, any hospital or university department involved in clinical pharmacy or pharmacology, clinical toxicology, or epidemiology can serve as the initial setting for pharmacovigilance activities. Reporting of adverse medicine reactions can begin locally, perhaps in a hospital, and later be expanded to other hospitals and health centers in the region, moving step by step to the national level. In some countries, pharmacovigilance centers are set up by professional associations, such as national medical societies.

4.2.4. Necessary Equipment

The technical infrastructure can be very simple. For communication, at least a telephone, e-mail address, or fax is needed to receive reports. Online systems are easy to use for reporting and reduce the need for hiring staff to input the data.

The equipment consists of:

- Multiline telephone (!!!).
- Computers with the characteristics necessary (hardware and software) to carry out the center's activities (database, text processor) (!!!).
- Printer (!!!).
- Scanner (!!!).
- E-mail (!!!).
- Photocopy machine (!!).
- Website (!!).
- Access to specialized databases procured on the basis of the selection plan and needs (!!).

In addition, the technical infrastructure must be sufficient for entering reports in a computer database. Finally, all systems should offer technical support to users that require assistance with paper or online forms (1).

4.2.5. Staff

Working in a pharmacovigilance center requires knowledge of clinical medicine, pharmacology, toxicology, and epidemiology. The competencies for assessing reports on cases of adverse reactions can be acquired by training center staff or recruiting expert advisers on a continuing basis.

Sometimes, however, a new pharmacovigilance center begins operations with only a single part-time expert (!!!), usually a pharmacist or doctor, and some type of administrative support. Shortly thereafter, it may be necessary to appoint a full-time expert as head of pharmacovigilance and to broaden the work of the Secretariat.

When reports of adverse reactions increase, staffing requirements can be calculated by estimating the average time it takes to process each individual report, which will depend on the center's infrastructure.

Ideally, a national coordinating center needs at least the following personnel (!!):

- A pharmacist, doctor, or a pharmacoepidemiologist;
- Administrative staff;
- A programmer or systems analyst, as necessary;
- A data processor, as necessary;
- Experts or consultants, as necessary;
- New professionals from the health sector that are beginning their training in the specialty.

Pharmacovigilance centers or units should put together an organizational chart that clearly indicates posts and their place in the organizational structure and defines the responsibilities and tasks of the staff and designated teams. Therefore, when organizing the work, the following should be considered:

- The center's organizational chart indicating posts and their place in the organizational structure (!!!);
- Job descriptions, indicating the basic functions, duties, responsibilities and the place of posts in the organizational structure (!!);
- The professional qualifications of each technical staff member, which should be those required by the standards of pharmacovigilance system (!!!) and reflected in the respective résumés;
- Written instructions for each post (!!);
- Adequate prior training and the planning of ongoing training in good pharmacovigilance practices and quality assurance procedures (!!!).

4.2.6. Service Continuity

Access and service continuity (!!!) are fundamental to good operation of a pharmacovigilance center. Consequently, the center needs a permanent secretariat to handle the phones and mail; maintain the database; handle scientific documentation, and coordinate activities. The continuity of the secretariat can be ensured through collaboration with other related departments, whenever there is sufficient capacity to do so (see section 6.6.2.);

4.2.7. Advisory Committees

It is a good idea for the center has a multidisciplinary advisory committee to support the pharmacovigilance center (!!) and provide technical assistance in the various specialties, ensuring the quality of procedures in:

- Data collection and assessment;
- Data interpretation;
- Publication of the information.

An advisory committee can be made up of specialists in the fields of general medicine, clinical pharmacology, toxicology, epidemiology, pathology, medicine regulation and quality control, medicine information, phytotherapy, vaccines, etc. Moreover, it is very useful to have a network of experts from the different specialties. If the center is situated in a hospital, it is easier to obtain specialized advice (see section 6.6.4).

4.2.8. Information Service

A basic responsibility of any pharmacovigilance center is to offer high-quality information services (!!), which also implies incentives for reporting. To this end, and for assessing the individual cases reported, the center should have access to databases with independent, up-to-date information (the UMC can provide a list of relevant bibliographic references).

Putting the center in a major hospital offers the advantage of facilitating consultations in the library. National pharmacovigilance centers can enjoy direct online access to the UMC database. Furthermore, medicine and adverse reaction bulletins published by WHO and certain national or regional centers around the world can be on the e-mail contact list.

Information on what has been learned from the reports should be provided to the professionals that sent them (!!!). Feedback of this type fuels and strengthens the reporting process, because it acts on the data generated and encourages continued reporting; lack of feedback can discourage people from reporting again.

The information service should also urge (!!!) communities, hospitals, universities, and professional associations to create, design, and develop active pharmacovigilance programs for special populations (children, the elderly, pregnant women, people with prevalent pathologies) and the medicines they need.

4.3. Documentation

Complete up-to-date documentation is at the heart of any quality assurance system and good pharmacovigilance practices. Its importance lies in the fact that reports can trigger signals; thus, the quality of the reporting is critical for proper assessment of a potential causal relationship between a medicine and adverse events.

4.3.1. Characteristics of Reports

Spontaneous reports on suspected adverse medicine reactions are currently the main source of information in pharmacovigilance. As mentioned in the Introduction, in some countries, reporting of suspected adverse reactions is voluntary, but in others, regulations are in place that requires health professionals to submit reports, although it is unusual to impose fines for failure to do so. In some countries, pharmaceutical companies are required to report suspected adverse reactions to the health authorities.

Methodologies for active pharmacovigilance are as important as spontaneous reporting, since they provide relevant data on special populations and medicines. Some examples of these techniques are prescription event monitoring (PEM), case-control surveillance, and record linkage between different databases. Finally, data on consumption or use are important for evaluating the safety of medicines. There is no doubt that promoting these types of programmed studies is essential to improving patient safety and that they should be conducted in conjunction with spontaneous reporting.

Adverse event reporting by the national pharmacovigilance system is voluntary, spontaneous, and confidential. It is especially useful in detecting signals of rare, serious, or unexpected adverse reactions.

The individual case report is used in pharmacovigilance always refers to a report about a patient who has experienced an adverse medical event (or an observed alteration in laboratory tests) that is suspected to have been caused by a medicine. The report is made on a reporting form or yellow card (see model in Annex II), as well as other printed forms for reporting international adverse effects, to indicate treatment, care, or precautions. Any suspected therapeutic failures associated with medicines marketed in the Region are also reported. The content of the cards may differ from country to country, but all have four sections that should be completed: patient information, description of the event, medicine information, and notifier information.

This is the basic information (!!!) that reporting forms should contain:

1. Patient information: weight, age, sex, and a brief clinical history (when relevant); in some countries, ethnicity is specified;
2. Description of the adverse event: nature, location, and intensity, including the date that the signs and symptoms appeared, their progression, and the outcome;
3. Information on the suspect medicine: generic or patent name, dosage, route of administration, treatment start and end dates, indications for use, expiration date, lot number, and manufacturer;
4. Data from the patient on his disease: health status before starting the medication, co-morbidities, relevant family history of disease;
5. Concomitant medicines. All other medicines taken by the patient (including self-medication): names, dosage, route of administration, start and end dates;
6. Information on the notifying professional. The name and address of the notifier should be considered confidential and used only to verify or complete the data or follow-up on the case.

It is both desirable and advisable (!!) to obtain the following information:

7. Risk factors (for example, altered kidney function, exposure prior to taking the suspect medicine, known allergies, use of recreational medicines);
8. Documentation on the diagnosis of the event, including the procedures used to obtain the diagnosis;
9. The clinical course of the patient and outcome (hospitalization or death). Patient outcome might not be available when the report is sent. In such cases there will be a follow-up;
10. Laboratory findings (including blood levels) corresponding to the start of treatment, the medication period, and subsequent therapies;
11. Information on the response after the medication is suspended, and re-exposure;
12. Any other relevant information (e.g., additional details related to the event or information on benefits received by the patient, if important for assessing the event).

Concerning reports on medication errors, correct reporting should include complete the following information (!!), when available:

13. Products involved: including the patent name and manufacturer, dose, dosage form, and types and size of containers;
14. Sequence of events leading up to the error;
15. Work environment where the error occurred;
16. Characterization of the personnel involved in the error, types of errors, and possible contributing factors.

There is no universal reporting form for spontaneous reporting systems (WHO found that it would not be an effective strategy). Thus, only guides indicating the basic data needed for the design of reporting forms have been prepared, as described in the paragraphs above. The principles should be applicable in any language (13).

Many regulatory authorities believe that it is important to include a narrative section to convey the meaning of the observations, since this will make it possible to capture the breadth of the context and sequence of events and to study the conditions in which the error or effect should be examined and understood. In fact, some believe that only narrative reports are capable of providing significant information about the effects caused by the event (9). Systems that include open narratives require additional resources for the analysis and interpretation of the data, unlike those with standardized forms, fixed fields, and predefined choices, in which the data are read, rapidly entered, and easily classified, thus lowering the overall cost of the analysis.

Another consideration is the impact of the reporting on the notifier. Giving notifiers the opportunity to describe the case means that their observations are valuable. When a notifier can count on receiving a measured and nonpunitive response, he feels that he is heightening the state of alert on patient safety, thus increasing his responsibility to report.

A national pharmacovigilance system can include some a mandatory reporting, which will be applied to medicines subject to intensive surveillance. This category includes medicines that are useful in the treatment of certain diseases but can produce serious side effects because of their characteristics. Therefore, reports are issued not only are for adverse effects of medicines in the general population, but in special populations as well; for example, the elderly, children, pregnant women, and patients with certain diseases.

In regard to active pharmacovigilance studies, there is the design of forms and questionnaires at the same time as the study objectives and number of patients in the study. In this case, other relevant data will be included, such as:

- The patient's study identification number;
- Neighborhood, district, and city in which he/she lives;
- Contacts;

The details to be entered will depend on the study, as in the case of the Pharmacovigilance Program for Antiretrovirals in poor countries (the questionnaires used can be consulted in the bibliography) (9).

Reporting should be as easy and economical as possible. Special forms can be distributed to professionals in the selected regions (for example, four distributions per year). It may be a good idea to include envelopes or other forms of prepayment in national formularies, medicine bulletins, or professional journals. Other expeditious reporting methods are telephone, fax, e-mail, and online forms, when there is Web access.

4.3.2. Other Documents

In addition to yellow cards, other documents are necessary for good operation of a pharmacovigilance center, among them quality manuals, operating procedures, and files or records.

To ensure good pharmacovigilance practices, it is essential to have documentation with the following characteristics (14):

- They must be designed, prepared, reviewed, and distributed on the basis of their usefulness;
- They must be approved, signed, and dated by the appropriate authorized personnel;
- They must be written unambiguously; their title, nature, and objective must be clear and they must be distributed in an orderly, easily verifiable fashion;
- Reproductions of documents must be clear and legible, and the introduction of errors and distortions in materials taken from original sources must be avoided;
- All documentary entries must be periodically reviewed and duly updated. When a document is modified, care should be taken to prevent information deleted from previous versions from reappearing;
- Documents should not be handwritten; however, if data need to be introduced, they can be entered by hand clearly and legibly in indelible ink. Enough space should be left for additional data;
- Any changes in written the data must be signed and dated; changes should not prevent the original data from being read. If necessary, the reason for the change will be indicated;
- Documents connected with the same report of a suspected adverse reaction should be kept in the same file or, in its absence, clear reference should be made to their location, so that important activities related to the report and its documentation or assessment can be monitored;
- There should be a record book containing the number assigned to the report, dates of reporting and entry, data on the origin of the report, and a brief description of the adverse reaction and the medicines. It will also contain other data, such as an imputability algorithm, communications with the author of the report, and other comments. This book can be generated from a computer database;
- The data can be entered through electronic data processing systems, photographic systems, or other reliable methods. However, detailed information on procedures for the system used should be kept, and the accuracy of the entries should be verified. If the documentation is processed electronically, only authorized personnel may enter or change the data on the computer, and a record should be kept of any alterations or deletions. Access should be restricted with passwords or other security measures, and it should be possible to verify independently the results of introducing basic data.
- The confidentiality of data on the patient and the author of the report should be preserved with codes. Electronically stored report files should be protected through back-up copies, so that data can be easily accessed as long as they are kept;

The activities connected with the receipt, follow-up, analysis, and transmission of a report on a suspected adverse reaction should be properly recorded, so that the data and criteria related to these processes can be verified at any time. In these entries, the confidentiality of the data identifying the patient and the author of the report must also be maintained.

4.3.2.1. Manuals

- Quality Manual: Describes the objectives, methods, and procedures for assuring quality. It is an important document that enables internal and external personnel to learn about the existing quality assurance system.
- Manual of procedures: Provides an orderly and logical description of the standard operating procedures used at the center and the relationships among them to give readers an idea of the overall quality assurance system.

4.3.2.2. Procedures

A written description of the activities involved in reporting a suspected adverse reaction is necessary. In order to decide whether a particular process has been well-executed, it must be held against an existing standard.

The operating procedures for the work (also known as SOP, for *standard operating procedures*) are a very important part of the documentation in any quality assurance system. They are defined as detailed; the written instructions for achieving uniformity in carrying out a specific activity and are the basis for internal or external audits.

Written procedures, as well as standards for data entry, must be available (!!!) to provide orientation for the following activities:

- Collection and transmission of information:
  - Receipt of reports;
  - Validation of the information;
  - Documentation of the adverse reaction;
  - Acquisition of complementary information;
  - Transmission of the report.
- Administrative activities:
  - Entry of data in the database;
  - Documentation file;
  - Protection of computer files;
  - Data modification.
- Assessment and preparation of reports:
  - Acceptance and rejection of reports;
  - Preparation of feedback;
  - Assessment and coding of reports;
  - Preparation of reports;
  - Prevention of duplication;
  - Detection and management of signals or alerts.

All operating procedures must include at least the following data (!!!):

- Name of the procedure and code assigned to it;
- Date of its final draft;
- Name and signature of the person who prepared it;
- Name and signature of the authority who has approved it;
- Name and signature of the person responsible for quality assurance;
- Name of related operating procedures;
- Circulation of copies: it is important to identify the people, departments, or sections that should receive copies.

4.3.2.3. Additional Documentation

Additional documentation is anything that complements the information in the form containing the data on adverse reactions. It can include information of telephone conversations with the reporting party; supporting documents (whether hard copy or electronic); copies of medical reports; copies of complementary tests, correspondence related to the report, the assessment report, the coding report, a report by an expert, etc. This documentation should be stored in the same file as the original report as long as the file is kept.

4.4. Computer Systems

When computer systems are used, they must be validated (!!!). Procedures must be used that include the following operations:

- General operations;
- Maintenance;
- Security;
- Control of access and back-up copies.

Back-up copies of the information must be made on a regular basis (!!!). The records shall be kept for at least five years, or the period stipulated in the legislation of each country. Moreover, there should be a list of personnel authorized to enter and modify the data; only they will have access to the documentation, and a record should be kept of any time the data is accessed (!!!).

Any alteration of the original data during processing should allow access to the earlier data and respective comments and guarantee the traceability of that information. The reason for the change should be indicated and kept on record (!!!).

Periodic monitoring of data quality should be performed in order to detect systematic data coding and processing errors (!!).

Center directors will decide which computer software to use (they can obtain information and assistance in this regard from the UMC). The database should have the necessary fields for assessing the case analysis and follow-up. Using software created in-house to process reports on adverse reactions may not be cost-effective. Good commercial software is on the market that can be adapted to local needs and the language of the user.

4.5. Management of Reports

Managing all the information from a center requires human resources with technology tools (!!!) that will permit continuous timely feedback that is valuable to the notifiers to encourage reporting and contribute to the analysis and investigation process.

Managing reports implies that when the national pharmacovigilance center receives the yellow cards or other forms used for local reporting, it does the following:

- Assesses all reports sent by health professionals. When the report comes from a professional who is not a physician, complementary information should be obtained from the prescriber or the patient's physician. When the report comes from a patient or another person who has taken the medication, it is important to contact the physician involved, if there is one, to obtain more detailed information;
- Confirms that the report contains the minimum information required to be considered valid: an identifiable notifier (name, address, and profession); an identifiable patient (name and/or clinical history, sex, age, date of birth); and identification of one or more suspect medicines and one or more adverse reactions. It is also important to know the date that the adverse reaction began;
- Makes the utmost effort to obtain complete and necessary information depending on the characteristics of the adverse event. This basic information makes it possible to generate signals or alerts but is insufficient for assessing the event. If the initial report is not in writing, it should be validated;
- Follows up on incomplete reports, especially when they refer to serious or unexpected adverse events, in order to obtain complementary information from the initial author of the report or documentation, such as hospital reports, laboratory results, the specialist's report, prescriptions, etc;
- Establishes procedures to encourage reporting among health professionals, with particular emphasis on reports of unexpected or serious adverse reactions and reports involving medicines that have recently come out on the market.

In the initial stages of a center's operations, case reports can be processed manually. When the number of reports increases, it is recommended that a computer system be used for data processing and the respective follow-up on the suspect medicines and adverse reactions.

The computer system should include a hierarchical index of medicines that permits their classification by generic component, patent name, and therapeutic category. Analogously, terminology that hierarchically classifies adverse reactions should also be used. This is necessary for entering the specific record with detailed information on the case and also for compiling the information by higher levels (12) (the recommended coding is found in section 4.5.3. Data Coding and Recording).

4.5.1. Submitting Reports

The way in which reports are submitted (e-mail, fax, Internet, regular mail, telephone) varies with the local infrastructure and technology:

- Regular mail, fax, and phone calls are the most widely used methods, since they are usually the most available (!!!);
- There should be a systematic processing procedure in place for reports received via e-mail or the Internet—if possible, one that is fast and easy to use, although the necessary technical infrastructure can be expensive (!!).

4.5.2. How to Improve Reporting

Procedures should be established to promote reporting among health professionals (!!!). These include:

- Facilitating easy access to yellow cards (or forms, tickets, files) with prepaid postage, and other means of reporting such as e-mail or a website;
- Acknowledging receipt of each report of a suspected adverse reaction through a personal letter or phone call to thank the author of the report;
- 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 the 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.

4.5.3. Data Coding and Entry

Procedures for data coding and entry for the center should be effective and functional.

- The pharmacovigilance system should use the coding and terminology categories (!!!) adopted in international regulatory forums (such as the International Conferences on Harmonization).
- The coding should be follow the practices outlined in the respective manual;
- The national or coordinating center should periodically monitor the quality of the data in order to identify possible systematic coding and entry errors (!!!);
- Data management should protect the identity of the people involved (!!!), both the author of the report and the individual who experienced the event, as defined in Section 4.3.1.

4.5.4. Characteristics of Reporting

- The integrity, accuracy, reliability, consistency, and confidentiality of all information must be guaranteed (!!!);
- For each report, the date of receipt should be recorded and an identification number assigned (!!!).

The internationally-accepted terminology for medicines and adverse reactions should be used.

- The names of medicines should be systematically recorded, using, for example, the *WHO Drug Dictionary*, which is based on the International Nonproprietary Name (INN) nomenclature and the WHO Anatomical Therapeutic Chemical (ATC) classification;
- For the coding of adverse reactions, either the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA) should be used to facilitate international comparisons of the results and their distribution to the other countries.

Special care should be taken to comply with the compatibility requirements of the WHO Program for International Medicine Monitoring. As mentioned earlier, detailed instructions can be requested from the Uppsala Monitoring Center (UMC) on how to organize the computerized data from each report for its transmittal to the WHO database. MedDRA has recently become part of Vigibase (the UMC database). This is a very important step for detecting signals (15) and aiding information exchange, education, training, and the investigation and assessment of adverse reactions.

4.5.5. Review of the Database

A database of reports on suspected adverse medicine reactions is an important source of information for detecting safety signals, as it can prompt the need for studies to confirm, characterize, quantify, and assess those signals. To this end, it is necessary for local and institutional databases to be linked to databases containing regional and global information for the pharmacovigilance purposes described in section 4.5.3.

Pertinent steps should be taken to avoid duplicate reports in the database. Before entering data into the database, the duplicate cases identified should be combined into a single case, following the guidelines of the International Conference on Harmonization (ICH) E2B (M).

The necessary measures should also be adopted to guarantee the security and confidentiality of the information on adverse events (!!!), regardless of how it is recorded (on paper, electronically, etc.) and the processing of pharmacovigilance data.

This will be assessed as follows:

- When uploading the information to database it is very important to verify that all data fields have been completed as indicated in the database instructions (!!!);
- The seriousness of the patient's condition will be entered as the principal adverse event (!!!);
- Define causality: The WHO definition and the Naranjo and Food and Medicine Administration's (FDA, USA) algorithms (Annex III) will be used to evaluate the causal relationship between a suspected adverse medicine reaction and pharmacotherapy;
- Review: The designated center will review the data from peripheral centers, homogenizing the information that will be sent to the National Center twice monthly (on the 15th and 30th). Only one transmittal will be made in December, on the 20th;
- The national database can be used for periodic reports, research on adverse medicine reactions, education, feedback to the system, requests for information, and final theses for undergraduate, master's, or doctoral degrees, always respecting the principle of confidentiality (!!).

4.5.6. Assessing Reports

Expert analysis and the dissemination of lessons learned are required if the reports are to impact safety. Mere data collection contributes little to improving patient safety. Expert analysis and supervision of the data are necessary to track follow-up trends. *The response system is more important than the reporting system* (9).

The following aspects are addressed when assessing case reporting:

- *Quality of the information:* This involves the completeness and integrity of the data, quality of the diagnosis, and monitoring. The basic elements of an individual report are outlined in sections 4.3.1, Characteristics of Reports, and 4.5, Management of Reports.
- *Coding:* As mentioned earlier, medicine names should be systematically recorded using the *WHO Medicine Dictionary* or its ATC classification. For coding adverse reactions, WHO-ART or MedDRA will be used (see section 4.5.3, Coding and Data Entry).
- *Importance:* Regarding the detection of new reactions, medicine regulation, and educational or scientific value, the following questions in particular, should be answered:
  - *New medicine:* Commercial medicines that have been on the market for less than five years are normally considered "new medicines".
  - *Unknown reaction:* For example, a reaction not included in the authorized fact sheet or Summary of Product Characteristics (SPC). It is also important to know whether the reaction is described in the

literature (for example, in the National Formulary, Martindale, or *Meyler's Side Effects of Medicines*) and to consult the UMC about any history of the reaction in other countries.

  - *Serious reaction:* This is the gravity of the effect of an adverse reaction on an individual. It may be classified as mild, moderate, or severe, depending on the effect (or lack thereof) on the daily activities of the patient.

- *Identification of duplicate reports:* Certain characteristics of a case (sex, age or date of birth, dates of exposure to the medicine, etc.) can be used to identify a duplicate report;
- *Evaluation of causality or imputation:* Different procedures have been developed to determine the probability structure of a causal relationship between exposure to medicine and adverse effects, among them that of the WHO Program for International Medicine Monitoring (*see* Glossary). These procedures are based primarily on the following: *the time* between administration of the medicine and the event, *medical or pharmacological plausibility* (signs and symptoms, laboratory tests, pathology findings, mechanisms), and the *likelihood or exclusion* of other causes.

For a complete assessment of the reports, the following questions must be answered:

- *Is there an alternative explanation for the reaction observed?*
- *Were other medicines administered that were not indicated in the report?*
- *Is it certain that the patient followed the indications when taking the medicine?*
- *Had the patient taken this medicine or another similar one before?*
- *How many cases of this new reaction have been reported to the regional or national center or the UMC?*

This information is not found on all cards, but efforts can be made to obtain it by contacting the notifier by telephone or e-mail. The data usually requested refer to potential underlying illnesses, other medicines taken by the patient that might not have been mentioned in the original report, the effects of that medicine or similar medicines taken on a previous occasion, and other relevant information (such as the dosage, the manner in which the medicine was administered, the length of the treatment, age). Additional information is usually requested when the reports describe severe illness, previously unknown adverse reactions, or medicines recently used as part of treatment.

4.5.6.1. Chronology

The time between the start of treatment and the onset of the first manifestations of the adverse reaction can be determined as follows:

- Administration of the medicine prior to the appearance of the episode described, if the timing is compatible with the medicine's mechanism of action and the physiopathology process of the adverse reaction.
- Administration of the medicine prior to the appearance of the episode described, but the timing is not fully consistent with the pharmacology of the preparation and/or the physiopathology process; for example, agranulocytosis that appears three months after suspension of the medicine. There is not enough information to determine the chronology or temporal relationship.

According to the data in the report, there is no reasonable temporal relationship between the administration of the medicine and the appearance of the adverse reaction, or the timing is incompatible with the mechanism of action and/or the physiopathology process (for example, a neoplasm that appears a few days after treatment begins).

4.5.6.2. Causality

For assessing the cause-and-effect relationship (causality and imputability), the Naranjo et al. algorithm is applied (Annex III). It consists of a probability scale that includes the time elapsed between the administration of the suspect medicine and the onset of the clinical symptoms. Also included is the plausibility of the causal relationship (taking the description of the reaction found in the medical literature or the known pharmacological properties of the medicine into account). Other areas involved are the course of the reaction after the medicine is withdrawn, the eventual repetition of the clinical episode described with re-administration of, or re-exposure to, the suspect medicine, and the potential existence of alternative causes. It can also include the existence of additional information

from complementary research designed to rule out other non-pharmacological etiologies. It has the advantages of being internationally accepted and user-friendly. Annex III contains the Naranjo and FDA algorithms.

According to the Naranjo algorithm, suspected adverse reactions are divided into four categories: 1) certain, 2) likely, 3) possible, and 4) unlikely.

It is reasonable to postulate that in some instances, the symptoms do not represent an undesirable effect of the medicine involved, although there is a temporal relationship and no alternative cause. In that case, a "conditional" causality category would be added.

Certain: A clinical event, including abnormal laboratory test results, occurring in a plausible temporal relationship to medicine administration, which cannot be explained by concurrent disease or the effects of other medicines or chemicals. The response to suspension or withdrawal of the medicine (sometimes known as "dechallenge") must be clinically plausible. The event must be definitive from a pharmacological or phenomenological standpoint, using a conclusive re-exposure (rechallenge) procedure, if necessary.

Likely: A clinical event, including abnormal laboratory test results, with a reasonable time lapse since administration of the medicine, unlikely to be attributable to concurrent disease or other medicines or substances and that yields a clinically reasonable response when use of the medicine is suspended (dechallenge). Information on re-exposure (rechallenge) is not required to meet this definition.

Possible: A clinical event, including abnormal laboratory tests, with a reasonable time lapse since administration of the medicine, but that can also be explained by disease that is concurrent or the effects of other medicines or substances. Information on the suspension of the medicine may be lacking or unclear.

Unlikely: A clinical event, including abnormal laboratory test results, with a time lapse since administration of the medicine that makes a causal relationship improbable, and in which the effects of other medicines, substances, or underlying disease offer explanations that are more plausible.

WHO includes a fifth category:

Conditional: The time lapse is reasonable, and the reaction cannot be explained by the patient's clinical status, but the symptoms are not known to be an undesirable effect of the medicine used.

Effect of suspending use of the suspect medicine:

- The undesirable effect fades with the suspension of the medicine; regardless of the treatment begun, (this obviously excludes cases of a single administration). The recovery period is compatible with the pharmacology of the medicine and the physiopathology process.
  - The reaction does not fade with the suspension of the medicine (lethal reactions obviously excepted).
  - Use of the suspect medicine has not been suspended, and the case does not improve.
  - Use of the medicine has not been suspended and the case improves, but the development of tolerance should be ruled out.
  - There is no information in the report about suspending the medicine.
  - The adverse reaction proves lethal, or the undesirable effect turns out to be irreversible. It is important to include birth defects related to administration of the medicine during pregnancy.
  - Even though use of the medicine was not suspended, the case improves owing to the development of tolerance.

Effect of readministering the suspect medicine:

- Accidental readministration of the medicine or its readministration under controlled conditions is a test with great diagnostic value, although in the latter case it may be ethically objectionable. The re-exposure can be:
  - Positive: The reaction recurs with readministration of the suspect medicine.
  - Negative: The adverse medicine reaction does not recur.
  - There was no re-exposure, or readministration of the medicine was not reported.
  - The undesirable effect has irreversible consequences (death, birth defects, or reactions that leave permanent sequelae).

Existence of an alternative cause

- Alternative causes such as the following are also assessed.
  - The alternative explanation is etiologically more important than the causal relationship with the medicine;
  - There is a possible alternative explanation, but it is less important than the possible adverse reaction to the medicine;
  - There is not enough information in the report received to assess the alternative explanation;
  - There is not enough information to rule out an alternative explanation;
  - This assessment brings together all the information necessary to determine the existence of a causal relationship between the medicine and the adverse reaction.;

4.6. Pharmacovigilance in Clinical Studies

Sections 6.16 and 6.17 of *Good Clinical Practices* of PAHO sets the standard for safety information and reports on adverse medicine reactions, stating that the study's sponsor is responsible for the ongoing safety assessment of the products being investigated. In addition, the *Good Clinical Practices* of PAHO must promptly notify all pertinent investigators/institutions and the regulatory authority of findings that may adversely affect the safety of subjects in the study. This is either because they affect the conduct of the trial or may alter the approval/favorable decision by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) to continue the trial.

The sponsor must promptly report any serious or unexpected adverse medicine reaction to all pertinent institutions and investigators, the IRB/IEC, where appropriate, and the regulatory authority, sending periodic updates and safety reports. These reports should comply with the applicable regulatory requirements.

Local regulations should stipulate the time required for reporting both expected and serious/unexpected adverse events. Reporting periods should be short; for example, in the case of serious and unexpected adverse events, the report should be filed within 72 hours at the latest.

Reports from clinical trials should be sent or identified separately from events attributable to medicines already on the market.

5. Good Risk Analysis and Risk Management Practices

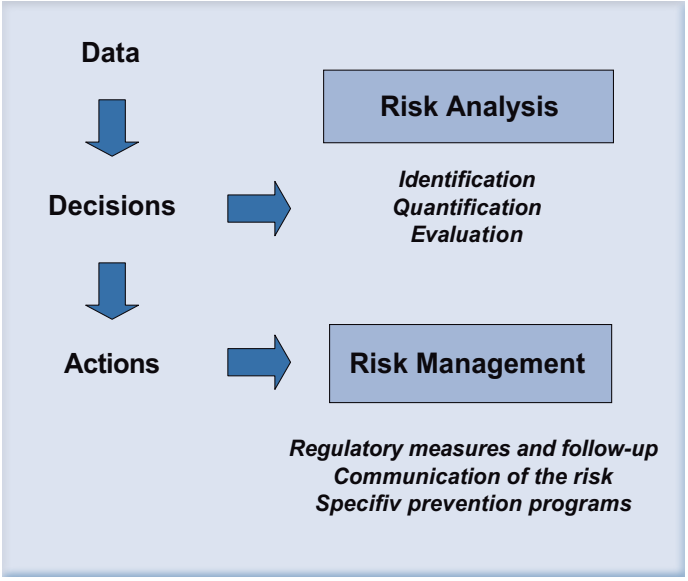
Pharmacovigilance primarily involves the identification of alert or safety signals. It also studies and manages the risks connected with medicines once they have been authorized for sale. Thus, two phases can be distinguished: risk analysis and risk management.

Risk analysis involves the identification, quantification, and evaluation of risks, and risk management, implementation and monitoring of the regulatory measures adopted to communicate risks to health professionals or the public at large and determine the preventive action to take. Risk analysis is driven by data and risk management, by action. The decisions made are the bridge between the two areas (Figure 1) (16).

Once the data have been entered using good practices, a three-step risk analysis is performed, and risk management begins:

- Identification of risks and the generation of signals;
- Quantification of risks;

Figure 1. Risk Analysis and Risk Management Diagram



Source: Francisco J. de Abajo Iglesias, División de Farmacoepidemiología y Farmacovigilancia, Agencia Española para los Medicamentos y Productos de la Salud, Presentation at the XI International Conference of Regulatory Authorities (ICDRA), February 16-19, 2004, Madrid.

- Risk assessment
- Risk management;
- Risk communication.

5.1. Identification of Risks

The identification of risks primarily involves the generation of signals and the evaluation of causality through individual case reports or a series of case reports.

A signal is the information communicated about a potential causal relationship between an adverse event and a medicine when that relationship is unknown or not well documented. A safety signal or alert indicates concern about the presence of more adverse events than would be expected or associated with the use of a product (11). Signals usually indicate the need for investigations to confirm or rule out the conclusion that the medicine had caused the event. Once a signal is identified, it should be evaluated to determine whether it poses a potential safety risk and whether other steps should be taken.

Signals generated through voluntary reporting (or other methods) should be evaluated, and a careful review of cases and search for other cases conducted. Signals can come from post-marketing studies or other sources or from preclinical data and events associated with other products of the same pharmacological class. They are detected chiefly by:

- Descriptions of isolated cases;
- The publication of cases in biomedical literature;
- Spontaneous reports to the pharmacovigilance system;
- Observational studies in populations: cohort or case-control studies;
- Experimental studies: clinical trials.

A single well-documented reported case can be viewed as signal, especially if it describes positive re-exposure or the event is extremely rare in the absence of the medicine in question.

5.1.1. Descriptive Analysis of a Series of Cases

A causality investigation of the individual events and the possibility that one or more cases might represent a safety concern meriting additional investigation will be conducted.

In evaluating the causal relationship between the use of a medicine and the appearance of the adverse event, the following will be considered (!!!):

- The appearance of the adverse event within the expected time period; for example, an allergic reaction that occurs during treatment, or cancers that develop years after the treatment;
- The absence of symptoms linking the event to the exposure;
- Evidence of positive discontinuity of the treatment or positive re-exposure;
- The consistency of the event with the known pharmacological/toxicological effects of the medicine, or in the case of vaccines, with the established immunological mechanisms of the injury;
- The consistency of the event with the known effects of other medicines of the same class;
- The existence of other supporting evidence (preclinical studies, clinical studies, and/or pharmacoepidemiologic safety studies);
- The absence of alternative explanations for the event; for example, the absence of concomitant medicines that could have contributed to the appearance of the event); or the absence of comorbid or premorbid medical conditions.

As part of the case review, it is suggested that all the clinical information on each case be evaluated and there is follow-up through the notifiers. It is important to eliminate duplications. Special attention should be paid to characteristics suggestive of a causal relationship between use of the medicine and the adverse events.

The categories recommended and employed by WHO in causality assessment should also be considered:

- Certain;
- Likely;
- Possible;
- Unlikely;
- Conditional.

If a series of cases is detected, a descriptive summary of the clinical information is recommended in order to characterize the potential safety risk and identify, insofar as possible, potential risk factors. A series of cases normally includes an analysis of the following (!!):

- Clinical manifestations, laboratory results, and the progression of the event;
- Demographic characteristics of the patients in relation to the events (for example, age, sex, race);
- Length of exposure;
- Time from the beginning of exposure to the product to the adverse event;
- Dosage used with the cases, including labeled dosage, the highest dosage for use, and the toxic dose;
- Use of concomitant medications;
- Presence of morbidity, particularly when the cause of the adverse event is unknown; also, if liver levels are low and a deterioration in kidney function is observed;
- Route of administration (for example, oral vs. parenteral) and the lots used with the patients who have experienced the events;
- Changes in the proportion of event reporting during a specific time period or the product's life cycle;

5.1.2. Use of Data Mining to Identify Associations between Medicines and Adverse Events

Data mining consists of extracting previously unknown information from databases that can be useful for some process or purpose. It includes a series of techniques for obtaining processable knowledge from large databases. In other words, data mining prepares, probes, and analyses data in order to extract the hidden information within. For an expert, or the head of a system, the most important thing is not normally the data itself, but rather the information contained in its relationships, fluctuations, and interdependencies.

In the various steps involved in the identification and assessment of risks, the systematic examination of adverse event reports through the use of data mining can furnish additional information about the existence of reported adverse events involving medicines (11). The application of these techniques to large databases, such as the adverse event reporting system of the Uppsala Monitoring Centre (UMC), Spanish Pharmacovigilance System, Adverse Reactions Data (FEDRA), the Adverse Event Reporting System (AERS) of Food and Drug Administration (FDA) (17), and the Vaccine Adverse Event Reporting System (VAERS)(18), can lead to the identification of an unusual or unexpected medicine-related adverse event that will prompt future investigations.

Data mining can be used to enhance strategies for the detection of existing signals and is especially useful for evaluating patterns, trends, and events associated with medicine interactions (!!). It also provides additional information about signals and their potential probabilistic distribution, using tools such as the Gamma Poisson Shrinker Program algorithm (19, 20) or Bayes' theorem.

Data mining cannot be used to establish causality between a product and adverse events. Its usefulness lies in permitting the identification of unusual or unexpected events, as it yields timely information for the investigations under way (!!) on:

- New adverse events not indicated on the product label, especially if they are serious;
- An apparent increase in the severity of an event indicated on the product label;
- An increase in the frequency of unusual serious adverse events;
- New interactions between medicines, medicines and food, or medicines and food supplements;
- Previously unrecognized at-risk populations (for example, risk attributable to specific racial or genetic predispositions or comorbidities);

- Real or potential confusion about the name of a medicine, its labeling, packaging, or how it is used;
- Concerns about the way a medicine is used (for example, its association with adverse events, potential deficiencies in quality or therapeutic effectiveness, labeling with high dosages indicated, or use by populations for whom the medicines are not recommended);
- Concerns about the possible implementation of inadequate risk minimization plans;
- Other concerns detected by current surveillance systems.

The results obtained with these methods will be analyzed by a multidisciplinary group of experts (!!!). Current data mining methods make it possible to set priorities through point system that, for a specific medicine, compares the proportion of reports of a particular event (for example, liver failure) and the proportion of reports observed with the proportion of reports of the same adverse event for all medicines (21).

The score generated quantifies the disproportion between the observed and expected values for a particular medicine-event combination. A potential excess of adverse events is defined as any medicine-event combination with a score that exceeds the specific threshold.

This should also be carefully studied in the epidemiologic context, which includes:

- A description of the database used;
- A description of the data mining tools used (algorithm, adverse medicine-related events, and stratifications of the analysis); an appropriate reference; and
- A careful individual evaluation of case reports and other relevant safety information related to a medicine-event combination of interest; for example, preclinical outcomes, pharmacoepidemiology, and other available studies.

The problem of incomplete observations—patient drop-outs, failure to follow up, etc.— often comes up when estimating the frequency of adverse reactions. Although there are statistical methods for dealing with this type of observation, they are not ordinarily used in calculating the frequency of adverse reactions. Missing data are simply ignored, which probably results in more optimistic estimates (22).

Another issue that arises is that, except when they are serious or even lethal, these reactions can occur repeatedly in the same patient, in which case, in addition to considering the number of patients with adverse reactions, it is also necessary to indicate the number of times they occur.

These problems and estimating the probability of an adverse reaction that has not yet occurred are discussed in detail in an FDA publication (23).

5.2. Generation of Signals

It is the responsibility of pharmacovigilance personnel to periodically evaluate the information in the database in order to detect signals:

1. The signals found will be discussed at meetings of the coordinating center, where the importance of taking them up with the regulatory authority will also be considered (!!!);
2. When it is determined that the signal detected constitutes an imminent public health problem, all pharmacovigilance centers should promptly be notified (!!!);

Two examples which shows the way the generation of a signal or alert prompted by spontaneous reports led to the recall of medicines are the cases of ebrotidine and cerivastatin (4, 24).

5.3. Quantification of Risks

5.3.1. Quantification of the Strength of Association

Once a potential new risk associated with a medicine has been identified, the next step will be to quantify the strength of the association between the adverse reaction and the medicine and its impact on public health (!!!). Although spontaneous reporting is usually a reasonable approach to the problem of a causal relationship between the medicine and the adverse reaction, it does not allow for quantifying the strength of the association or estimating the incidence with which it appears.

Data on the use of medicines will serve as a proxy for the denominator, expressed in months or years of treatment based on the daily average dosage or number of prescriptions, and using the number of cases, obtaining a figure to calculate the risk.

5.3.2. Studies to Quantify Risks

In most cases, this second step in risk analysis can be rigorously carried out only through analytic epidemiologic studies. Different designs can be used for post-marketing surveillance studies to quantify risks. The purpose of these studies will be to verify a hypothesis—that is, to establish causality between an alleged adverse reaction to a medicine and the use of that medicine. The studies may be observational analytic studies, which are divided into two major categories, depending on the patient selection criteria: cohort studies and case-control studies (see description in the Glossary}.

5.4. Risk Assessment

5.4.1. Assessment of the Benefit/Risk Ratio

The third step in the analysis is to judge whether the risk identified and quantified is acceptable to society and under what conditions. In addition to the data on the risk of the medicine, its potential benefit should be considered, along with the risks and benefits of any therapeutic alternatives, when they exist. Ultimately, the aim is to attempt to determine whether the benefit/risk ratio of the medicine continues to be favorable.

This ratio is difficult to quantify because, inter alia, benefit and risk are not usually expressed in the same units, as, for example, in the case of deaths prevented by the treatment vs. deaths caused by adverse reactions. However, even in this particular situation, it is highly probable that the number of deaths does not fully reflect the benefit of the medicine, the quality of life, or all the attendant risks. Another difficulty is that there is no clear definition of the line between what is acceptable and what is unacceptable, beyond the circumstance of each individual.

Assessing the benefit/risk ratio is a process that requires data, to which the element of value must then be added. Determining the social acceptability of associated risks requires technical assistance from individual experts or the ruling of expert committees made up of specialists (14), which will always consider:

- Supervision, approval, and advice in pharmacoepidemiologic studies;
- The systematic review of scientific literature and any other information on adverse medicine reactions and the active ingredients that are the object of the reports;

5.5. Risk Management

Risk management is an iterative process of assessing the benefit/risk ratio of a medicine. It consists of developing and implementing risk minimization tools while preserving the benefits. These instruments make continuous reassessment of the balance between benefits and risks possible and permit the respective adjustments to minimize the risks, with the resulting improvement in the benefit/risk ratio. This process should continue over the life cycle of the product. With the results of the risk assessment in hand, the people responsible for a product will make decisions to reduce the risks (14, 23).

The innovative concept of risk management systems in medicine regulatory bodies was introduced in the United States, and Japan, and the European Union, based on the International Conference on Harmonization's risk management guidelines for quality and pharmacovigilance planning. They represent an advanced stage of development in assuring the quality, safety, and efficacy of the products and processes that should be evaluated for inclusion in our context.

Once the risk analysis phase has concluded, the conditions will be right to take the timely effective action that we call risk management. From the standpoint of pharmacovigilance, there are three relevant actions:

- Adopting administrative measures for risk reduction;
- Communicating the existence of risk, the steps taken, and the pertinent recommendations to health professionals and patients;
- Adopting specific prevention strategies.

Risk management activities include (!!):

- Preparing, approving, and sending information inter-institutionally or to professionals and the general public;
- Managing the response to requests for information from notifiers and the general public;
- Communicating emergency restrictions on medicines for safety purposes and changing pharmacovigilance conditions for their authorization;
- Promptly evaluating and communicating any changes that affect the benefit/risk ratio of medicines to the pharmaceutical industry and health professionals;
- Coordinating capacity building, training, and technical assistance to members of the reporting network and health professionals;
- Disseminating information and essential knowledge to the general public about problems associated with medicines and the appropriate use of medicines.

5.5.1. Risk Minimization Plan

To ensure medicine safety and effectiveness, pharmaceutical laboratories must try to maximize benefits and minimize risk (!!!). For most medicines, risk minimization measures are sufficient. Such measures include an accurate description of the uses, safety, and efficacy of the medicine in the package insert, as well as continuous updates from post marketing studies on new benefits, changes in the formula, and new indications, if appropriate. However, it is both important and advisable to design a risk minimization plan.

This type of plan consists of a strategic safety program for meeting specific goals and objectives in order to reduce the known risks of medicines while preserving their benefits. It can also be regarded as a selective action plan for safety issues, as defined by the International Conference on Harmonization (ICH *E2E: Pharmacovigilance Planning*). Risk minimization plans are developed in the preclinical, clinical, and post-marketing phases of medicines. An effective plan can be implemented only with appropriate information about these phases, the intended use of the medicine, and the groups for whom the medicine is intended.

In order to achieve the goals—which will depend on the type, frequency, and seriousness of the risk—it is recommended that the plan consider specific and measurable practical objectives. A variety of strategies is currently used, which can be divided into three categories:

- Training for health professionals in risk communication and the adoption of safety guidelines, which implies specific organizational plans and training;
- Systems that make it possible to record processes and adopt modalities of use and prescribing practices that reduce risk—among them, training with evaluation, patient consent, and mechanisms for collecting pharmacy data;
- Access systems that offer guidance on the use, prescription, and dispensing of medicines to target populations, providing greater benefits and minimizing specific risks through prescribing by specialists, restricting sales to certain pharmacies, and dispensing to patients who have had laboratory tests;

When designing the plan, the analysis should be done on a case-by-case basis depending on the medicine in question, bearing in mind (!!!):

1. The nature of the medicine and the known benefit/risk ratio, evaluating the following:
   - The type, magnitude, and frequency of the risks and benefits;
   - High-risk populations, as well as those that stand to benefit the most;
   - The existence of treatment alternatives;
   - The reversibility of the adverse events observed;
2. The prevention of adverse events;
3. The likelihood of benefits.

Risk management plans will result in a regulatory document that will be submitted to the health authorities and agreed to by them, with a Periodic Safety Update Report (PSUR) or an independent report that meets the requirements of the health authority in each country.

When designing the plan, its cost-effectiveness should be evaluated.

5.5.2. Administrative Risk Reduction Measures

The national regulatory authority and the pharmaceutical laboratories, as the entities responsible for the authorization and marketing of the medicine, are in charge of taking the necessary steps to reduce the potential risks posed by its use. The decision to put regulatory measures in place should consider the social acceptability of the risk in relation to the benefit, although other factors tend to come into play when the available information is dubious or insufficient. The measures can range from reporting the new risk to immediate withdrawal of the medicine. The decision should be based on evidence, in addition to experience, objectivity, and transparency.

Administrative risk reduction measures, known as "health security measures," will depend on the risk detected, depending on the degree of the risk, can be classified as:

1. Imminent or serious health risk;
2. Acceptable risk when used under any conditions;
3. Acceptable risk only when used under certain conditions;
4. Unacceptable risk when used under any conditions.

1) In the case of *imminent or serious health risk*, the following measures will be adopted:

- Retention of lots of the medicine or the entire product on the market;
- Their quarantine;
- Temporary, partial, or complete suspension of activities or services;
- Temporary, partial, or complete closure of the pharmaceutical facility.

2) In the case of *acceptable risk when used under any conditions,* consideration will be given to keeping the registration status or marketing authorization, and the following steps will be taken:

- Inclusion of information in the fact sheet or package inserts (addition of information to clarify specifics of the adverse reactions, with treatment recommendations);
- Introduction of new information to indicate the proper use and administration of the product, the use of low doses, alternative therapies, or concomitant use of the medicine with another medicine to prevent risks;
- The necessary information will be communicated about this new introduction of the medicine, about evidence that the suspicions were unfounded and there is no risk to public health, and about the adoption of other measures to prevent risks.
- Release of lots (or all) of the product withdrawn from the market that was retained or held in quarantine.

3) In the case of *acceptable risk only when used under certain conditions*, modification of registration status or change in market authorization will be considered and the following measures will be adopted:

- Reduction of the recommended dose;
- Restriction of therapeutic indications; elimination of one or more indications;
- Introduction of new adverse reactions, contraindications, warnings, precautions, or medicine interactions;
- Elimination of information;
- Restrictions for certain population groups;
- Recommendation to conduct clinical or analytic follow-up tests;
- Restrictions on dispensing (for exclusive hospital use, prescription sale, use by certain specialties; medicines requiring special monitoring; programs with intensive monitoring, or for compassionate use);

– Restriction of prescription to certain specialties;
– Restrictions on dosage forms;
– Changes in the container;
– Changes in the dosage form;
– Changes in the formulation;
– Changes in the composition;
– Changes in the composition;
– Changes in storage or method of preparation.

4) In the case of *unacceptable risk when used under any conditions*, if the medicine is toxic or unsafe under normal conditions of use, and is not therapeutically effective, has an poor benefit/risk ratio, or for any other reason implies a foreseeable risk to people's health or safety, the sanitary safety measures will be:

– Recall of lot(s) of the product from the market;
– Recall of the product or its active pharmaceutical ingredient from the market; The recall can be immediate or progressive, at the request of the marketing authorization holder or by legal mandate. In all cases, this measure carries with it suspension or cancellation of the market authorization or temporary market authorization;
– Seizure;
– Destruction of the product;
– Fines;
– Diversion of the product to other uses, where appropriate;
– Temporary or permanent, partial or full suspension of the activities or services;
– Temporary or permanent, partial or full closure of the pharmaceutical facility.

5.6. Risk Communication

5.6.1. Periodic Safety Update Reports

Periodic safety update reports are official documents that contain all the pharmacovigilance data on a particular medicine in a given period, according to its registration date. The objective is for pharmaceutical laboratories to participate in the compilation of reporting data, evaluate the safety information compiled, and present it in a standardized way to the regulatory authority that approved the medicine. These reports present the national and international experience with the safety of a medicine, with the object of:

- Communicating all relevant new safety information from reliable sources;
- Presenting a summary of the marketing authorization situation in different countries and any important safety modification;
- Periodically facilitating the opportunity to reevaluate safety and decide whether the therapeutic information on the patent medicine needs to be modified;

People have the right to be accurately informed about the health risks of new technologies; only in exceptional cases, and to avoid a greater risk, can a failure to communicate some or all of the information be justified. This ethical approach is the most effective way to manage situations of risk. There is a certain consensus in pharmacovigilance that the most appropriate method of conveying information is to have health professionals be the primary recipients of information, which enables them to serve as a point of reference for potentially affected patients. Only after this first phase should the population be informed about the risk, either through the media or other mechanisms.

Marketing authorization holders who sell pharmaceuticals in each country are responsible for submitting periodic safety update reports to the health authorities at set times. According to the guidelines in the ICH E2C,

new periodic safety update reports should follow the specifications governing the content of the report and the international date of the medicine registration for the frequency of reporting, which will be every six months for the first two years, once a year for the next three years, and every five years thereafter.

5.6.2. Publication and Information in Pharmacovigilance

Information on medicine risks should be published and disseminated without delay. Once evaluated, this information should be communicated to the public through the appropriate channels. Information on suspected adverse reactions should be communicated promptly to health professionals, marketing authorization holders, pharmacovigilance systems or other institutions, and the medicine regulatory authorities.

- The medicine regulatory authorities should be notified about cases of adverse reactions caused by medicines or technologies, whose health risks should be communicated to the public;
- Before informing the public about the risks associated with a medicine, the media should make sure that, they have formally notified the respective institutions and health authority; to this end, they will request a reliable communication or authorization to this effect, in advance, from the competent government authority;
- Before publishing information about a case or a series of cases, publishers should be sure to notify the respective institutions and health authority, requesting a letter of confirmation or a notification of receipt of this information.

It is important to distinguish between the different situations that arise when a known risk or an emerging risk is involved. In the first case, informing the public should be part of the routine of daily clinical practice. The rule should be to provide information that is as complete as possible, always considering the particular situation of the patient and the extent to which he is willing to accept the risks, knowing what the preventable risks are and being aware that serious unexpected risks may arise from the use of the medicine. Complementary written information can be a great help, especially in the absence of a detailed package insert geared to the patient.

Regarding the second situation (emerging risks), there has been debate over how to best to inform the public so that it can make better decisions, without creating unnecessary panic or alarm. Now, however, there are no universally accepted guidelines to show the way and avoid improvised solutions, making this a pending issue for the majority of medicine regulatory authorities (MRA).

Information on the measures adopted will be disseminated through the appropriate communications channels, among them:

- Officially regulated labeling (primary container, secondary container, package insert, fact sheet or pamphlet, and summary of product characteristics);
- Letter of response to complaints and claims;
- Risk communications sent to health professionals;
- Resolutions on health measures to reduce risk;
- Printed bulletins or material distributed via e-mail or available online;
- Scientific articles;
- Public notices in the media (press, radio, television, Internet).

5.6.3. Crisis Management

A crisis can occur when news is published about product safety or efficacy issues that can have a significant public health impact and thus call for immediate action. A crisis can also occur when the media release reports expressing concern about the use of a particular product.

When a crisis occurs, the regulatory authority should study the available information and use it to make the pertinent decisions, such as applying appropriate regulatory measures, obtaining or issuing additional information, and communicating the risk or its absence, as the case may be. Whatever the case, there should be close cooperation with stakeholders and the ability to institute emergency measures when faced with evidence of risk and a public health impact (14).

When a crisis occurs, the medicine regulatory authority should take a series of steps to properly channel the information:

- Put the parties involved in contact;
- Coordinate with them as much as possible to ensure a consensus on the action to take and its application to the local level;
- Reach an agreement with stakeholders on a single communiqué for the public, including patients and health workers; if this cannot be done, the health authority will inform the public of its position on the issue.

To ensure that these objectives are met, the following steps should be taken (!!!):

1. Confirm that a crisis exists;
2. If necessary, begin managing it;
3. Obtain a rapid scientific assessment of the benefit/risk ratio of the crisis;
4. Determine the strategy to follow;
5. Based on the available reports, issue recommendations on the action that stakeholders should take;
6. If the regulatory agency decides that action should be taken, supervise the activities;
7. Prepare an action plan that includes supervision.

Whatever the case, the regulatory authority should establish a mechanism for communicating with the media, providing timely information to avoid speculation in the news and help manage the crisis from a security standpoint.

5.7. Risk Prevention

It is important to design prevention strategies, since many adverse events are the result of errors in usage and specific adverse reactions that could have been avoided (!!).

Risk prevention should be both systematic and periodic. Health professionals (physicians, dentists, pharmacists, nurses), consumers, pharmaceutical companies, and health authorities have a shared responsibility. Communication among them is key to systematic prevention. Intensive pharmacovigilance or monitoring programs can also be developed for specific medicines (e.g., clozapine) or risk groups (e.g., pregnant women, children, the elderly). In terms of unavoidable adverse reactions, the goal should be early detection, the primary prevention measure for reducing the extent of the harm. Information for health professionals and patients alike is undoubtedly the best strategy.

Mechanisms should be established to integrate health surveillance into health promotion and publicity about adverse reactions, warnings, and contraindications.

5.8. Evaluation of the Pharmacovigilance System

Evaluation should be built into the monitoring system. The national coordinating and review center should periodically evaluate system operations, and in whether and to what extent:

- Reports are complete, on time, and accurate;
- Responses have been rapid;
- Case management has been appropriate;
- Appropriate action has been taken to avoid mistakes'

Table 1 contains a list of the characteristics identified as essential for the success of an adverse event reporting system.

Ideally, certain criteria for evaluating the system must be selected; for example:

- The distribution of reports by category and specialty of the health professionals and patient typology;
- The quality of reporting: completeness of the information, accuracy of descriptions, value of the information for decision-making;
- Proportion of reports describing serious or unknown reactions;
- Timeliness of the reporting;
- Reporting indexes; for example, the number of cases reported per unit of population or per number of health workers;
- Assessment of the impact of adverse reactions on morbidity, mortality, and health expenditure (usually weighted by hospital admissions for adverse reactions).

Table 1. Characteristics of a Successful Reporting System

Non-punitive	Notifiers do not fear sanctions or reprisals;
Confidential	The identities of the patient, notifier, and institution are never revealed;
Independent	The reporting system is independent of any authority with the power to punish the notifier or institution;
Expert analysis	Reports are evaluated by experts who understand the clinical context and are trained to recognize underlying conditions;
Timely	Reports are promptly analyzed, and recommendations are rapidly disseminated to the people who need them, especially when serious threats are detected;
Systems-oriented	Recommendations focus on changes in systems, processes, or products, rather than individual performance;
Responsive	The agency receiving the reports is able to disseminate recommendations.

Source: Cited in World Health Organization. World Alliance for Patient Safety. WHO. Draft Guidelines for Adverse Event Reporting and Learning Systems: From information to Action. Geneva: WHO; 2005.

6. Functions and Responsibilities of Agents Involved

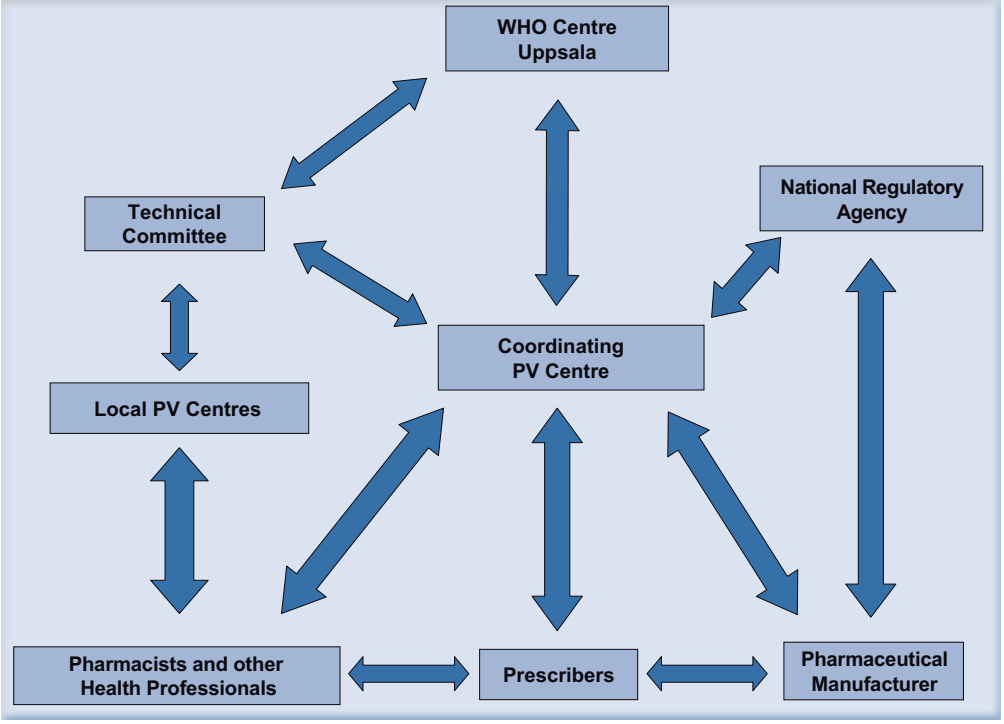
Pharmacovigilance is a cooperative effort and responsibility shared by all the agents and entities involved with the use of medicines: health authorities, pharmaceutical laboratories or marketing authorization holders, hospitals and universities, medical and pharmaceutical associations, nongovernmental organizations, toxic substance and medicine information centers, health professionals, patients, consumers, and the media. To ensure coherent development and prevent the overlapping of competencies and unnecessary duplication of efforts, effective collaboration, coordination, communication, and public relations among all stakeholders are necessary.

This section defines the objectives, functions, and relationships among the principal agents and entities involved:

- National regulatory authority;
- National pharmacovigilance systems;
- Health professionals;
- Pharmaceutical laboratories or marketing authorization holders;
- Other health institutions.

Figure 2 shows the linkage between the agents in a pharmacovigilance system; however, other linkage models also exist.

Figure 2. Relations among Agents in a Pharmacovigilance System



6.1. National Regulatory Authority

It is the responsibility of national governments to guarantee a supply of safe and effective quality medicines and their correct use. The public health agency should be aware of the risks of adverse reactions and their diagnosis, reporting, and management. Government resources are necessary for national coordination of pharmacovigilance. As mentioned earlier, multidisciplinary collaboration is very important, and it is essential for the health authority to forge the necessary ties between the different departments of the ministry of health and other relevant sectors involved in the rational use of medicines and pharmacotherapy control.

For satisfactory performance of those functions, the public health authority should:

- Create a national pharmaceutical regulatory agency—in this document, the "National Regulatory Authority" (NHA)—to draft legislation and/or regulations on pharmacological control that also cover medical devices or equipment, herbal remedies, and diagnostic reagents that could affect human health. If a regulatory authority already exists, the public health authority should actively promote its effective operation;
- Develop national policies and action plans;
- Create a national pharmacovigilance system;
- Designate or create an official national or coordinating center to study adverse reactions.

The national medicine regulatory authority should have an advisory or safety committee on medicines for human use that studies and evaluates the available evidence, research findings, and reports on adverse medicine events to support decision-making.

6.1.1. Essential Elements of Effective Pharmacovigilance

The elements essential to pharmacovigilance in a specific national medicines policy designed to meet health objectives are:

- Rational and safe use of medicines by health professionals;
- Appropriate assessment and communication about the risks and efficacy of medicines;

- Dissemination of basic knowledge, general information to patients, and specific information to health professionals.

The national regulatory authority should have the will and the ability to react to signals from the national pharmacovigilance system and centers, instituting the appropriate regulatory measures. Furthermore, it should monitor the impact of system or center activities through process and outcome indicators. It should also provide a steady stream of information on adverse reactions to professionals and consumers, as well as continuing education for health professionals.

The mission of the national regulatory authority is to protect health by monitoring the relative safety and efficacy of products designed to safeguard and restore health. This includes not only medicines and food, but cosmetics, diagnostic reagents, medical devices and equipment of all types, and products used nationwide that could affect health.

6.1.2. Activities

The authority should ensure that the following activities are carried out in connection with medicines it has approved, pursuant to current legislation (25):

- Reporting and management of suspected adverse reactions;
- Preparation and review of periodic safety reports;
- Timely and complete response to any request for information from the competent medicine safety authorities;
- Ongoing evaluation of the benefit/risk ratio during the post-marketing period and prompt communication of any information that could imply a change in the ratio to the competent authorities;
- Setting of criteria for identifying and assessing the seriousness of signals or alerts;
- Supervision of post-marketing safety studies;
- Periodic review of the scientific literature on spontaneous adverse reactions to the active ingredients that the manufacturer is authorized to market. Cooperation with pharmacovigilance centers on medicine safety issues.

6.1.3. Relations with Marketing Authorization Holders

The medicine regulatory authority will verify that pharmaceutical laboratories and marketing authorization holders have pharmacovigilance programs in place for marketed and investigational medicines. It should also require them to make all relevant information on the benefit/risk ratio of any of their products available in a timely manner, pursuant to the regulatory framework.

The regulatory authority will verify that trained personnel are responsible for the pharmacovigilance activities of pharmaceutical laboratories and marketing authorization holders and will put pertinent inspection procedures in place to ensure that the obligations contained in the section on the responsibilities of laboratories and marketing authorization holders are met (see Section 6.5). The regulatory authority can therefore audit any pharmacovigilance department in a laboratory and learn about its quality, suitability, and operations. Thus, the regulatory authority is empowered to take the appropriate corrective steps, require structural changes, and impose the pertinent sanctions under current regulations.

6.1.4. Certification of Good Pharmacovigilance Practices in the Pharmaceutical Industry

The national regulatory authority will issue a Certificate of Good Pharmacovigilance Practices and certify pharmaceutical companies that:

- Have pharmacovigilance programs that properly comply with the regulations in force and adhere to the guidelines for good pharmacovigilance practices established in this document;
- Attend and actively participate in the training activities programmed by the health authority;
- Demonstrate through their reports to the authority that their pharmacovigilance activities meet quality criteria.

Institutions with pharmacovigilance programs that have already been endorsed by international health authorities such as the FDA or the European Medicines Agency (EMEA) will automatically be certified, although they will have to attend the activities programmed by their local health authority.

6.2. National Pharmacovigilance System

Pharmacovigilance systems collect, analyze, and disseminate information on adverse medicine reactions and recommend the measures that should be adopted (6). They act as centralized agents, receiving reports from peripheral agents, health professionals, or consumers. They evaluate the reports and prioritize the information received in order to issue recommendations for the sectors involved in the health system on the risks and benefits of a medicine that have been identified, indicating all the pharmacological, therapeutic, and toxicology information that they have evaluated and considered disseminating. A pharmacovigilance system should be supported by the regulatory agency, as mentioned in Section 6.1.

The specific needs of each country's system will vary with the pharmacovigilance initiatives. The efforts required will depend on the respective system and infrastructure. Some countries already have well-established national pharmacovigilance centers, backed by a national regulatory authority. These countries have a public health department with an initiative that is vertically related to a specific health program. Other countries have public health departments that tend to use the same personnel to manage different programs for different diseases, and pharmacovigilance centers may be rudimentary or even nonexistent.

In organizing a pharmacovigilance system, there should be a clear sense of the questions that must be addressed before developing the work plan (!!!). Only with clear goals can an appropriate plan for data gathering and analysis be adopted (8). The strengths of a pharmacovigilance system lie in the development of new methods for evaluating medicine safety, including active studies and better analysis of data and signal detection processes. Another strength, which is of considerable importance to public health, is training and expertise in evaluating benefit/risk and communicating it to the public—an essential component of good pharmacovigilance practices, as well as an ethical imperative (26).

Functional requirements will vary from country to country and will depend on the respective health system and regulatory authority. However, it will always be essential to produce clear organizational charts indicating the functions and responsibilities of staff, the physical location, and the specific levels of responsibility (e.g., national, state, local level, primary health care centers, etc.).

Pharmacovigilance systems have the following functions:

- Planning, coordinating, evaluating, and implementing pharmacovigilance throughout the national territory;
- Establishing a coordinating center or national pharmacovigilance center whose primary functions are: to report, gather data, coordinate, investigate, and manage adverse medicine reactions across the country;
- Managing the database, evaluating causality, and analyzing the data;
- Promoting the formation of a national commission or committee on the safety of medicines for human use;
- Coordinating action with the regulatory agencies;
- Promoting good pharmacovigilance practices at the different organizational levels and throughout the nation;
- Coordinating action with the regulatory agencies;
- Training health professionals on the reporting of adverse reactions and all other aspects of pharmacovigilance;
- Promoting pharmacovigilance activities;
- Exchanging information and coordinating activities with other countries and international centers.

6.2.1. National Pharmacovigilance Centers

National centers with pharmacovigilance systems under them are responsible for:

- Serving as a reference center for the pharmacovigilance of medicines for human use;

- Receiving, evaluating, coding, and uploading to the pharmacovigilance database any reports on suspected adverse reactions and medicine-related problems forwarded by pharmaceutical laboratories or marketing authorization holders;
- Ensuring the safety and confidentiality of data and their integrity during data transfer;
- Coordinating the activities of each pharmacovigilance center in the country, in accordance with the established norms;
- Serving as the national pharmacovigilance system's representative to the pharmaceutical industry, pharmaceutical laboratories, or authorized marketers of medicines for human use;
- Ensuring that all reports of suspected serious adverse reactions in the country are recorded and publicized as soon as possible;
- Administering the database of the national pharmacovigilance system, ensuring its constant availability and updating;
- Guaranteeing the quality of the database;
- Developing methods for obtaining early warning signals;
- Coordinating the monitoring of articles on local adverse reactions published in national or international medical journals;
- Ensuring that the data from the collected reports were obtained through good pharmacovigilance practices, and avoiding to the utmost duplicate reports;
- If the pharmacovigilance center is new, establishing contacts with WHO in Geneva, Switzerland, and the UMC; it would also be useful to contact the national pharmacovigilance centers of other countries, whose experience would be useful for training new personnel;
- Serving as the national reference center in WHO's international pharmacovigilance system, sending periodic report on adverse reactions at least every two months and participating in meetings held by WHO on matters related to pharmacovigilance;
- Transmitting information on any regulatory measure stemming from a safety problem to therapy committees and all responsible agencies, pursuant to the procedures for risk communication;
- Conducting studies to evaluate the safety of medicines for human use;
- Promoting pharmacovigilance information and training in all health services in the country;
- Establishing procedures for dealing with infractions discovered through pharmacovigilance, as appropriate;
- Using the coding categories and terminology adopted in international regulatory forums (such as the International Conferences on Harmonization);
- Sending the results of the reports to notifiers (health professionals), as they are the backbone of the reporting system.

6.2.2. Local Pharmacovigilance Centers

Local centers or peripheral actors may be independent or spontaneously appear, but they must report to the national centers. Their functions include:

- Setting up, implementing, and strengthening the spontaneous reporting system and other programs in their geographical area, adhering to good pharmacovigilance practices;
- Receiving, evaluating and processing local reports of suspected adverse reactions in their geographical area communicated by public health professionals or the pharmaceutical industry, as well as those found in the scientific literature and authorized studies, when applicable;
- Reporting suspected serious adverse reactions to the coordinating center so that the information can be entered in the database of the national pharmacovigilance system no later than 10 calendar days after its receipt;

- Publishing and distributing reporting cards (yellow cards) for suspected adverse reactions and problems related to medicines to health professionals in their geographical area;
- Documenting and validating, insofar as possible, the information from reports on suspected adverse reactions, verifying its authenticity and consistency with the original documents available;
- Maintaining the reliability of the data from reports of suspected adverse reactions, using terminology as similar as possible to that used by the notifier;
- Safeguarding the confidentiality of the personal data on both patient and notifier;
- Responding or returning the results of reports to the professionals who sent them to encourage their participation;
- Filing and safely storing all reports sent on suspected adverse reactions;
- Developing methods for obtaining early signals or alerts;
- Contributing to scientific advances by improving pharmacovigilance methods, as well as knowledge and understanding of the nature and mechanisms of adverse medicine reactions;
- Responding to requests for information on adverse reactions from health professionals in their geographical area and keeping records on both the requests and the responses provided;
- Responding to requests for information from the health authorities;
- Promoting and participating in pharmacovigilance training activities for health professionals.;
- Participating in the meetings of the national pharmacovigilance system;
- Creating an internal quality assurance system that guarantees adherence to good pharmacovigilance practices.

6.3. Public Health and Immunization Programs

The pharmacovigilance system should work in coordination with the other public health and immunization programs, so that reports of adverse events and reactions are communicated to the Uppsala Monitoring Center for evaluation and remittance. Although submitted to public health entities, events supposedly attributable to vaccination and immunization (ESAVI) should also be communicated to the pharmacovigilance system, taking care not to duplicate reports.

6.4. Health Professionals

The effectiveness of a national pharmacovigilance system is directly dependent on the active participation of health professionals, who are in the best position to report any suspected adverse reactions observed in patients during their daily practice. All health professionals (physicians, pharmacists, nurses, dentists, etc.) should report adverse reactions as part of their professional responsibilities, even if they are in doubt about the precise link with the medication (27).

Originally, only physicians were asked to report adverse events, given their skill in determining, through differential diagnosis, whether the symptoms were due to medications or disease. It was also argued that medical data would ensure good quality and minimize the reporting of unrelated events. However, studies have shown that to detect a wider range of adverse reactions, all health practitioners must be involved. All sectors involved in health must participate: public and private hospitals, primary care centers, dispensaries and clinics, doctors' offices, pharmacies, and vaccination posts. The health professionals who work in these places are in the best position to provide a representative picture of the situation. Their functions include:

- Reporting all suspected or serious or unexpected adverse reactions and all those connected with recently marketed medicines, as well as problems related to the use of medicines;
- Promptly sending such information to the respective local or national center, by means of the yellow card spontaneous reporting system used by the national pharmacovigilance system;
- Keeping clinical documentation on adverse medicine reactions in order to complete or conduct monitoring, if necessary;

- Cooperating with the technical staff of the national pharmacovigilance system, providing source documents on request, in order to expand or complete the information on reported cases of suspected adverse reactions;
- Keeping up to date on the latest information about the relative safety of medicines that are regularly prescribed, dispensed, or administered;
- Collaborating with the people in charge of pharmacovigilance in pharmaceutical laboratories or with marketing authorization holders by providing information on request, after learning of the existence of an adverse reaction in a patient who has used a medicine.

In cases where patients directly report an adverse reaction to a national or local center, it is useful to consider the possibility of contacting their physicians to obtain additional information and verify the data.

6.5. Pharmaceutical Laboratory or Marketing Authorization Holder

The pharmaceutical manufacturing laboratory or marketing authorization holder is legally responsible for the safety of its medicines. Therefore, it must ensure that for suspected adverse reactions to the products it manufactures are reported to the competent national authority. It must also have an adequate pharmacovigilance system so that it can exercise its responsibilities and obligations with respect to the medicines it is authorized to market and ensure that appropriate steps are taken, when necessary. Although, it is the national regulatory authority in each country that determines the responsibilities of these entities, their basic duties include:

- Reporting all suspected serious adverse reactions received from a health professional through the pharmacovigilance system within the period stipulated by the authority in each country (generally, within 15 days of receipt of the report);
- Keeping detailed records on all suspected adverse reactions that it has learned of, which should be reported to the national regulatory authority;
- Designating a qualified professional to take charge of pharmacovigilance tasks on a continuous and ongoing basis, providing adequate means to exercise his or her functions; this professional will also serve as the liaison with the regulatory authority and should be the only spokesperson recognized by the competent public health authorities when it comes to pharmacovigilance;
- Proposing timely changes to the fact sheet file, labeling, and package insert when adverse reactions not listed in the material occur;
- Ensuring that all laboratory technical staff receive the training required for the exercise of their Pharmacovigilance functions;
- Transferring some or all of its functions and responsibilities to another company, but not the ultimate pharmacovigilance responsibility for monitoring the medicines it is authorized to market;
- Establishing agreements on pharmacovigilance issues in cases where a joint marketing agreement among several companies has been negotiated. Any transfer of pharmacovigilance functions and responsibilities must be documented through a written agreement signed by company representatives. Functions not transferred under this agreement remain the responsibility of the marketing authorization holder. Any transfer of functions and responsibilities must be reported to the respective health authorities;
- Facilitating the designated professional's access to the fact sheet and basic safety information for each pharmaceutical product approved, ensuring that they are properly updated;
- Ensuring that appropriate standardized work procedures are adopted and followed;
- Guaranteeing a filing system which permits the preservation of all documentation on pharmacovigilance responsibilities and activities. The responsibilities for managing the files must be stated in writing;
- Establishing an audit program to ensure that the pharmacovigilance system follows good practices.

6.6. Other Health Institutions

The growing body of scientific knowledge on medicine safety can be attributed to the growing awareness and interest of academia. The worldwide efforts of clinical pharmacology and pharmacy departments have led to the

development of pharmacovigilance as a clinical discipline. Hospital and university pharmacology and pharmacy centers have played a major role through teaching, training, clinical research, ethics committees, and clinical services, as well as policy-making.

6.6.1. Hospitals and Other In-patient Centers

Adverse medicine reactions that lead to hospitalization or the prolongation of hospital stays have a significant public health and economic impact; nevertheless, there is marked underreporting of these events, due in part to the limited participation in reporting activities of most professionals in hospitals and in-patient facilities.

Hospitals are tremendously important for pharmacovigilance, not only because of the high incidence of medicine-related hospital admissions but because of the high incidence of lethal adverse reactions, as seen in a number of international studies. Pharmacovigilance in hospitals should be the responsibility of a pharmacoepidemiologist, or in his or her absence, the technical director of the hospital pharmacy, whose main responsibilities will be:

- To distribute reporting forms to all health professionals in the hospital;
- To receive, assess, and process reports of suspected adverse reactions submitted by hospital health professionals;
- To complement information that is unavailable and necessary for expanding the search for a possible signal or alert by contacting the notifier;
- To identify the valid reports and send them to the coordinating center, discarding the invalid ones; efinir las notificaciones válidas y pasarlas al centro coordinador, desechando las no válidas;
- To send the reports on fatal or serious cases at the hospital to the coordinating center within 24 hours;
- To maintain the confidentiality of personal data on both patient and notifier;
- To review the reports received and purge duplicates;
- To increase and review the available scientific literature in the field of adverse medicine reactions;
- To propose and conduct pharmacoepidemiologic studies in the hospital to assess the medicine safety profile;
- To respond to requests for information on adverse reactions from hospital personnel;
- To promote and participate in training activities in hospital pharmacovigilance and pharmacoepidemiology for health professionals and technical staff;
- To respect the standards and procedures established by the country's health authority;
- To provide feedback to notifiers of adverse reactions.

6.6.2. Universities

An important aspect of pharmacovigilance is training health professionals in undergraduate and graduate programs. Appropriate training activities can improve their knowledge and understanding of adverse medicine reactions and encourage reporting. The curriculum of medical, pharmacy, dentistry, and nursing programs should include pharmacovigilance.

Pharmacovigilance centers can contribute by participating in graduate programs. The hypotheses or findings of the pharmacovigilance system can be topics of potential interest for additional studies on mechanisms, the frequency of reactions, and other aspects. The epidemiology or pharmacology departments at universities and other institutions can take advantage of these studies (12).

Implementation of a pharmacovigilance system is always strengthened by partnerships with pharmaceutical laboratories, academic institutions, and the regulatory authorities, which promote the development of pharmacovigilance (3).

6.6.3. Medicine and Toxicology Information Centers

Medicine and toxicology information centers have much in common with pharmacovigilance centers, in organizational and scientific aspects. If pharmacovigilance is implemented in a country that already has a toxicology or medicine information center, it would be a good ideal to collaborate closely with it. Costly installations and services,

such as the services of a secretariat and computer and library resources, can be shared. In any case, collaboration is a desirable objective.

Medicine information centers and local or national formulary committees, in turn, can benefit from collaboration with the pharmacovigilance center.

6.6.4. Medicine Safety Committee

Medicine safety committees are generally professional bodies that advise the national medicine regulatory authority and allied agencies on medicine safety issues. These committees evaluate safety concerns that arise with marketed medicines and suggest measures for lowering the risks detected. A committee's composition may be flexible and should, insofar as possible, include prominent professionals from groups in the national network, academic institutions, and international pharmacovigilance bodies whose actions are governed by regulations.

A presenter is named for each topic. This expert, who may or may not be a member of the committee, prepares a report and presents it for discussion. Pursuant to the rules, when the committee recommends a substantial change, revocation, or suspension of the marketing permit for a pharmaceutical product, it is its responsibility to inform the respective pharmaceutical laboratory of its right to a hearing before the Committee. In the event that the pharmaceutical laboratory wishes to exercise this right, a meeting with the Committee is convened, where an oral presentation is given on the issue under discussion. Agreements reached in the Committee will be adopted by the head of the medicine regulatory authority, and the affected pharmaceutical laboratories will be notified in writing.

The Committee functions are:

- To evaluate the benefit/risk ratio of medicines as a result of safety problems (this is the Committee's main responsibility);
- To propose studies and research on pharmacovigilance issues;
- To collaborate in the coordination, planning, and development of the pharmacovigilance system and in the assessment of post-marketing studies;
- To provide technical assistance to representatives of the national regulatory authority who attend PAHO working groups and meetings on pharmacovigilance issues;

6.6.5. Professional Associations of Physicians and Pharmacists

Many associations, including medical or pharmaceutical associations, have monitoring systems to follow adverse reactions and medication errors. These associations provide current information in their respective fields and can also provide infrastructure to facilitate studies and training for personnel.

6.6.6. Consumer Organizations and the Media

Support from national consumer organizations and patients' rights groups can contribute to general acceptance of pharmacovigilance, promote the reporting of incidents, and defend patients' rights.

Good relations with prominent journalists can be very useful, for example, for public relations in general and as part of a risk management strategy any time an acute medicine-related problem arises. Special precautions should be taken when explaining the limitations of pharmacovigilance data to journalists (see Section 5.6: Risk Communication).

Glossary of Concepts and Terms Used in Pharmacovigilance

Abuse. Intentional excessive, permanent, or sporadic use of a medicine that is accompanied by harmful physical or psychological effects (28).

Adulterated medicine. For legal and regulatory purposes, an adulterated medicine is considered to be: a medicine that does not have the same definition or identity in terms of its physical-chemical properties as attributed by the official or reference pharmacopeia. A medicine that does not have the identity, purity, potency, and safety as the name and qualities announced on its label. Other definitions include; a medicine that is sold in packaging or wrapping not allowed by regulations, since it is deemed that hazardous substances may be added to the medicine or react with the medicine in a way that changes its properties. A medicine that contains coloring or other additives technically deemed hazardous for this particular type of medicine; a medicine that has been manufactured, handled, or stored under unauthorized conditions or conditions that do not comply with regulations (35).

Adulteration. Harmful modification of the content or nature of a medicine, biological, medical device, or dietary supplement caused by a manufacturing process that does not adhere to good manufacturing practices (29).

Adverse Drug Reaction (ADR) According to WHO, “a harmful and undesirable reaction that occurs after administration of a medicine, at doses usually used in the human species, in order to prevent, diagnose, or treat a disease, or change a biological function.” Note that this definition implies a causal relationship between administration of the medicine and the onset of the reaction. “An undesirable effect attributed to administration of...” is currently preferred, and the original WHO definition is reserved for the concept of adverse event, which does not necessarily imply a cause-and-effect relationship. It should also be noted that this definition excludes poisoning or overdose.

Response to a medicine that is harmful and unintentional and occurs at the dosage usually used in human beings. In this description, it is important to consider that patient response is involved, individual factors can play an important role, and the phenomenon is harmful (e.g., an unexpected therapeutic response can be a side effect but not an adverse reaction) (13).

Adverse Effect (*see also* “Adverse medicine reaction”). Synonym of adverse reaction (29).

Adverse Event. Any untoward medical event that occurs during treatment with a medicine but does not necessarily have a causal relationship with such treatment. In this case, the event occurs at the same time as treatment but there is no suspected causal relationship (12).

Adverse Event Reporting System (AERS). The database of the computerized FDA adverse event reporting system designed to corroborate the safety assessments of the post-marketing programs for all approved medicines and biologicals (12).

Adverse Incident (AI). An injury or potential risk of unintentional injury to the patient, operator, or environment that occurs as a result of using a medical device or apparatus (*see* “Medical Device Vigilance”) (39).

Adverse Reaction Mechanisms. HAccording to the classification put forward by Rawlins and Thompson, adverse reactions produced by medicines can be subdivided into two major groups based on the production mechanism: those that are normal but heightened pharmacological effects (Type A or *augmented*), and those that are abnormal and unexpected pharmacological effects if the pharmacology of the medicine is taken into account (Type B or *bizarre*). (*see* Type A effects, Type B effects, Type C effects, and Type D effects).

Alert or signal. Information communicated about a potential causal relationship between an adverse event and a medicine when this relationship was previously unknown or not fully documented. Usually more than one report is required to generate a signal, depending on the severity of the event and the quality of the information (29).

Algorithm. Systematic decision-making process that consists of an orderly sequence of steps, in which each step depends on the result of the preceding step. The use of algorithms in clinical decision-making tends to reduce interobserver variability (30).

Allergic Medicine Reaction. An adverse medicine reaction that is dose-dependent and mediated by the immune system. Allergic reactions are divided into four main clinical types:

- **Type 1 reaction**. Known as immediate anaphylactoid or hypersensitivity reaction, is mediated by interaction of the allergen (medicine) and IgE antibodies. Reactions caused by the administration of penicillin are an example of this type of reaction.
- **Type 2 reaction**. Cytotoxic reaction—that is, a complement-fixation reaction between the antigen and an antibody present on the surface of some cells. These reactions include medicine-induced hemolytic anemia, agranulocytosis, and other reactions.
- **Type 3 reaction**. A reaction mediated by an immune complex deposited on the cells of the target organ or tissue.
- **Type 4 reaction**. The result of direct interaction between the allergen (medicine) and the sensitized lymphocytes. It is also known as delayed allergic reaction and includes contact dermatitis (12).

Alternative cause. In assessing the causal relationship, when there is an explanation, an underlying condition, or another medicine taken at the same time that is more likely than the causal relationship with the medicine studied (30).

Analytic study. A study designed to examine associations, whose ultimate purpose is usually to identify or measure the effects of risk factors or specific health interventions. Analytic studies can be controlled clinical trials, cohort studies, case-control studies, or cross-sectional studies (29).

Anatomical, Therapeutic, and Chemical Classification (ATC). System for coding medicines and medication according to their pharmacological effect, therapeutic indications, and chemical structure. At the first level, it includes 14 major groups of systems/organs. Each group in the first level is subdivided into four more levels; the second and third levels are pharmacological and therapeutic subgroups; the fourth level refers to the therapeutic/pharmacological/chemical subgroups, and the fifth level designates each medicine (31).

Beneficial. Effect of a therapeutic intervention that is considered favorable to the patient. Beneficial effects may be sought or unexpected (29).

Benefit (therapeutic). This is usually stated as the proven therapeutic effects of a product, although it should also include the patient's subjective evaluation of such effects (30).

Benefit/risk ratio. Reflects the ratio between the benefits and risks associated with the use of a medicine. It is used to express a judgment about the function of the medicine in medical practice, based on data about its efficacy and safety and considerations about factors such as potential improper use or the severity and prognosis of disease. The concept can be used for a single medicine or for comparisons between two or more medicines used for the same indication (29).

Bias. Systematic shift in all observations obtained about a sample with respect to their real or accepted value. It is also used to refer to a systematic or consistent error in test results or an influence on sample selection that makes the sample unrepresentative with respect to a given variable (33).

Bioethics. Clinical research ethics. For a clinical trial or another study to be ethical, the following must occur: (1) there must be reasons to question which strategy has the most favorable risk/benefit ratio (*equipoise*) or, if a treatment is only being tested, to presume that its benefits outweigh its risks; (2) there must be proper design and qualified investigators; (3) participants must be fully aware of the consequences and freely and voluntarily participate. According to by D. Gracia, the four basic bioethical principles are respect for persons, beneficence, justice (stated in the Belmont Report), and doing no harm (30).

Biological. A medical product based on biological material of human, animal, or microbiological origin (e.g., blood products, vaccines, insulin) (29).

Biological plausibility In assessing causal relations in epidemiology, when the association found is consistent with the available experimental biological knowledge (29).

Case-control study. A study in which persons with a certain disease or symptom (cases) are compared with other persons who do not have the disease or symptom studied (controls) in terms of prior exposure to risk factors. Such studies are, by definition, retrospective. In a case-control study a single disease is studied, but several risk factors or exposures are considered (29).

This design is especially useful when studying adverse reactions that are infrequent or require long exposure periods or induction to appear, since the inclusion of a sufficient number of cases is guaranteed without the need to follow all the subjects in the source population from which the cases are derived, as would occur if a cohort-type design were selected.

Another advantage of these case-control studies is that they permit analysis of the disease's association with several factors at the same time. Frequently used in case-control studies is a measure of association known as the "odds ratio" (OR). If the control patients are a random sample from the source population, it is easily shown that the OR and relative risk (RR) coincide.

It is important to emphasize that while passive monitoring, spontaneous reporting, is really valuable, active monitoring is necessary, since it offers greater sensitivity for the identification, confirmation, characterization, and quantification of potential risks. Active pharmacovigilance activities include the design and development of post-marketing use and/or safety studies that permit a more formal approach to risk prevention.

Causality (*see also* "Imputability"). Causality categories can be based on the results of imputability analysis and individual evaluation of the relationship between administration of a medicine and the onset of an adverse reaction.

Causality categories. The causality categories described by the Uppsala Monitoring Center are as follows:

- **Certain**. a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to medicine administration, and which cannot be explained by concurrent disease or other medicines or chemicals. The response to withdrawal of the medicine (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- **Likely**. a clinical event, including laboratory test abnormality, with a reasonable time lapse following administration of the medicine, unlikely to be attributed to concurrent disease or other medicines or substances, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenging of information is not required to fulfill this definition;
- **Possible**. a clinical event, including laboratory test abnormality, with a reasonable time lapse following administrations of the medicine, but which could also be explained by concurrent disease or other medicines or chemicals. Information on medicine withdrawal may be lacking or unclear.
- **Unlikely**. a clinical event, including laboratory test abnormality, with a temporal relationship to medicine administration which makes a causal relationship improbable, and in which other medicines, chemicals or underlying disease provide plausible explanations;
- **Conditional/Unclassified**. a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination;
- **Unassessable/Unclassifiable**. a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified (12);

Classification of adverse events, by severity:

Serious adverse event. In clinical studies, any untoward medical situation associated with a medicine that at any dosage causes death, threatens life, or leads to or prolongs hospitalization. It results in persistent or significant disability. It is a congenital anomaly, birth defect, or any situation classified as medically significant. All other adverse events in which these characteristics are not present will be classified as not serious.

Expected/listed serious adverse event. A serious adverse event whose specificity or severity is consistent with what is described in the investigator's brochure, basic prescribing information, or product label;

Unexpected/unlisted serious adverse event. A serious adverse event whose specificity or severity is inconsistent with what is described in the investigator's brochure, basic prescribing information, or product label;

Clinical significance. Probability that an observed difference will have an impact on the course of the problem or disease treated that is relevant for a given patient or group of patients. It should not be confused with statistical significance: descriptions of statistically significant differences that are not clinically significant often occur (29).

Cohort event monitoring studies. Modeled after prescription event monitoring (PEM) studies, which have been used with contraceptives in China, New Zealand, and the United Kingdom. The WHO program to monitor antiretrovirals in developing countries has recently been implemented using this model in the developing countries (9). Cohort event monitoring studies are intensive pharmacovigilance studies designed to obtain systematic and complete quality information on suspected adverse medicine reactions; the information is characterized by its high sensitivity and reliability, especially when it is necessary to determine the frequency of adverse reactions and identify predisposing factors and patterns of medicine use, among other things.

The term includes observational, or prospective, cohort studies on the use of medicines in patients who are the target population for that medicine. In this case, all adverse events are included, not just those in which adverse reactions are suspected. This makes these studies particularly effective in identifying unexpected and previously unrecognized adverse reactions.

There are two basic requirements for data collection: establishing a cohort of patients for each medicine and/or combination of medicines; and recording the adverse events of patients in the cohorts over a set period of use of the medicine. The cohorts must be complete and as representative as possible. Recording all adverse events is essential to keep any new signals from missing. In these cases, appropriate monitoring procedures should be designed and put in place to obtain information on any adverse event and train personnel in the methodology.

These studies have many advantages, since they produce indexes as well as a complete description of the profile of adverse reactions to the medicines in question and its characterization in terms of age, sex, duration, and risk factors. They make it possible to obtain records on pregnancies and all deaths, and produce rapid results for specific populations (9). These advantages are helpful in overcoming the deficiencies of the spontaneous reporting system, although the system is still essential because it covers the entire population and its duration is open-ended. The two systems are complementary.

Cohort study. A study in which individuals subjected to a certain exposure or treatment are compared with others who have not been treated or exposed. The term “cohort” (from the Latin *cohors*) means company of soldiers. There are prospective cohort studies and retrospective cohort studies; consequently the term is not a synonym for prospective study. In a cohort study, a single medicine or group of medicines is studied, but several diseases are considered (29).

Cohort studies, which are observational and analytic in nature, make it possible to calculate incidence rates of adverse reactions induced by the medicine. Two types of cohort studies can be distinguished: closed and open. Closed cohort studies do not allow patients to modify their exposure, and the patients are followed over a fixed period of time. Static populations are used. Its measure of frequency is the cumulative incidence (number of new cases divided by the population that generates the cases). Open cohort studies, in contrast, use dynamic populations (naturally existing populations), in which subjects can modify their exposure (a single subject can contribute to periods of exposure and nonexposure), and the monitoring time is variable. Its measure of frequency is the incidence rate (number of new cases divided by the sum of the observation periods for each subject).

Cohort studies permit the direct estimation both of measures of association (relative risk) and frequency (absolute risk). They also make it possible to estimate the attributable risk (difference between exposed and unexposed incidences), a measure of considerable interest from a public health standpoint.

Confidentiality. Respect for the secrecy of the identity of the person for whom a suspected adverse reaction has been reported to a pharmacovigilance unit, including all personal and medical information. Similarly, the personal information about reporting professionals shall be kept confidential. Throughout the entire pharmacovigilance data collection process, the necessary precautions must be taken to ensure the safety and confidentiality of data, as well as its integrity during the data processing and transfer processes (28).

Confounding factor. A variable that is independently associated with the risk factor and the disease studied at the same point in time and can alter the outcome of the study. Such variables should be identified and their influence avoided. Thus, for example, in a study that aims to evaluate the relationship between the use of oral antidiabetics during pregnancy and the potential for increased risk of birth defects, diabetes would be a confounding factor because it is associated with the use of oral antidiabetics and increased risk of birth defects (in this case it would be “confounding by indication”). When a certain variable is considered to be a confounding factor at the time of study design, interference can be avoided prior to data collection (by pairing or restriction) or during the analytic phase by stratification and multiple regression analysis (29).

Controlled clinical trial. The clinical research paradigm and basic tool are for evaluating the efficacy of medicines. However, its application in post-marketing safety assessments, however, is usually considered inefficient, except in cases where the safety problem is a sufficiently frequent clearly defined objective and above all, in the presence of confounding factors that are difficult to eliminate (especially confusion resulting from indication).

Counterfeit medicine. A product in which the identity or source has been deliberately or fraudulently labeled incorrectly. Counterfeiting can apply to patented and generic products, and counterfeit products may include products with improper ingredients, without active ingredients, with insufficient active ingredients, or with counterfeit packaging (35).

Cross-sectional study. An epidemiologic strategy in which observations about numerous factors are recorded at a single point in time and then compared. The presence or absence of disease and other variables (or, if they are quantitative, their level) are determined in each subject. The results can be analyzed in two ways: by comparison of all variables in individuals that have the disease studied, by comparison to persons without such disease, or by comparison of the prevalence of disease in different population subgroups defined on the basis of the presence or absence of certain variables. In a cross-sectional study, the time sequence of the facts cannot be determined; therefore, it cannot be known which came first, the onset of the disease in question or each of the variables considered (29).

Data sheet. A standard form containing essential scientific information about the proprietary medicine in question for distribution to health care professionals by the marketing authorization holder. It must be approved by the competent health authorities who issued the marketing authorization (28).

Descriptive study. A study designed for the sole purpose of describing the distribution of certain variables but that does not examine the associations between them. The study design is usually cross-sectional (29).

Dosage form. The physical form of the finished pharmaceutical product (e.g., tablets, capsules, syrups, suppositories, etc.). With the development of biopharmacy and specifically, the recognition of the importance of bioavailability, the importance of dosage forms as systems for the release or delivery of medicines or active ingredients has become increasingly evident. This has led to acceptance of the need to evaluate their suitability for release of the active ingredient, which is their primary characteristic (33).

Effectiveness (*see also* Efficacy and Efficiency). Degree to which a certain intervention leads to a beneficial result with the usual conditions of practice in a certain population (29).

Efficacy. Degree to which a certain intervention leads to a beneficial result under certain conditions, measured within the context of a controlled clinical trial. Demonstration that a medicine is capable of altering certain biological variables is not proof of clinical efficacy (for example, although some medicines can cause reduced blood pressure, this effect does not necessarily mean that they will be effective in reducing the cardiovascular risk of a hypertensive patient) (29).

Efficiency. Effects or results obtained with a certain treatment in relation to the effort employed in administering the treatment in terms of human resources, materials, and time (29).

Essential medicines. A group of medicines that are the basic, most important, indispensable medicines required to meet the health care needs of most of the population. This concept was developed by WHO to optimize the limited financial resources of a health system (36).

Excipient. A pharmacologically inert substance added to a medicine to give it shape, consistency, odor, flavor, or any other characteristic that makes it suitable for administration. In some cases, excipients cause undesirable effects, particularly allergies (33).

Facsimile medicine. A medicine marketed by a pharmaceutical laboratory not granted marketing authorization. This can only occur when there is no legislation on intellectual property rights (patents) in place. Basically, the legal protection of medicine patents can cover products or procedures; for procedures, a laboratory can manufacture any medicine that is protected by a procedural patent, as long as the method for producing the medicine is significantly different from that described by the inventor and the original manufacturer. Facsimile medicines are referred to by an alternative brand name (29).

FEDRA. Spanish Pharmacovigilance System Database of Adverse Reactions (28).

Fixed-dose combination. A pharmaceutical product that contains certain quantities of two or more active ingredients and suitable pharmaceutical technology (29).

Food and Drug Administration (FDA). Regulatory agency for food and drugs in the United States.

Generic (*see* Generic medicine) (12).

Generic medicine. A medicine distributed or dispensed with a label containing the generic name of the active ingredient (i.e., without identification of the patent name or trade name) (29).

Good pharmacovigilance practices. Set of standards or recommendations designed to guarantee the authenticity and quality of the data collected on medicine-related risks for ongoing evaluation; the confidentiality of the information on the identity of the persons that have had or reported adverse reactions, and the use of uniform criteria in the evaluation of reports and the generation of signals and alerts (28).

Harmonization. Process for seeking consensus on medicine registration requirements and procedures, as well as other matters regulated, in which regulatory authorities and the pharmaceutical industry participate (33).

Homeopathic medicine. A medicine used in homeopathic medicine, whose dosage form may be solid or liquid, and characterized by very low concentrations of the active ingredient. In the homeopathic system, there is the expression of concentrations in a decimal system of attenuation or dilution.

Hypersensitivity (*see* Allergic medicine reaction) (12).

Iatrogenesis. Abnormal or altered state caused by the activities of the physician or other authorized personnel. In some countries, the term has a legal connotation, as it refers to a situation caused by “improper treatment or treatment error” (33).

Imputability (see also Causality). This is a case-by-case analysis of the causal relationship between medicine administration and the onset of an adverse reaction. It is an individual analysis used for reporting purposes, as it does not seek to study the potential risk of the medicine overall or the importance of the risk associated with the medicine in the population. Imputability methods used are to harmonize and standardize the imputation process and to allow for reproducibility by different evaluators (28).

Incidence. This is a term which designates the different measures, in an effort to quantify the dynamic of an event in a group of subjects over a certain period of time (33).

Indication. The uses that a product (e.g., medicine, medical device, food supplement) is intended for once it has been scientifically demonstrated that its use for a particular purpose is safe and effective. In other words, the use is justified in terms of the product’s risk-benefit in terms of prevention, diagnosis, treatment, relief, or cure of a disease or condition. The indications are included in the product labeling when approved by the health authorities (33).

Indicator. A variable that reflects the health status of a community and can be measured directly (33).

Innovator medicine. Generally, this medicine, first authorized for sale based on its quality, safety, and efficacy documentation (36).

Intensity or severity of adverse reaction (see also Severity). This is the magnitude of the effect of an adverse reaction on an individual. There is the description of being as mild, moderate, or serious depending on whether or not and to what extent it affects the patient’s daily activities. It is different from “seriousness”, which assesses the risk to the patient’s life associated with the reaction (28).

Intensive pharmacovigilance. Pharmacovigilance method that consists of *systematically* obtaining complete, *quality information* on suspected adverse medicine reactions. It is characterized by high *sensitivity* and *reliability*, particularly when the frequency of adverse reactions, identification of predisposing factors, patterns of medicine use, or other items must be determined (28).

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Organization founded in 1990 that holds periodic conferences in which regulatory authorities and pharmaceutical associations from the United States, Japan, and the European Union participate, with other countries and WHO attending as observers. Its purpose is to prevent the duplication of preclinical and clinical trials because of differing regulations in different countries and, in general, to standardize medicine regulatory processes and monitor the pharmaceutical quality of medicines (32).

International Nonproprietary Name for Pharmaceutical Substances (INN). Name recommended by WHO for each medicine. Its purpose is to achieve standard identification of all medicines at the international level (29).

Lack of efficacy (therapeutic failure, therapeutic ineffectiveness). This is unexpected failure of a medicine to produce the expected effect as previously determined by scientific research (33).

Lethal serious adverse event. Any event that causes the death of the patient

Local pharmacovigilance center. The functional unit linked to the public health system, responsible for implementing official pharmacovigilance programs in a particular area: programming, coordination, collection, assessment, coding, training, and information on adverse medicine reactions.

Medical device (for human patients). This is a machine, (instrument, artifact, or article,) including its components, parts, or accessories, that is manufactured, sold, or recommended for use in: (1) the diagnosis, curative or palliative treatment, or prevention of a disease, disorder, or abnormal physical state or its symptoms; (2) the restoration, correction, or modification of a physiological function or bodily structure; (3) the diagnosis of pregnancy; (4) care during pregnancy or childbirth, or afterwards, including care for the newborn. Medical devices do not achieve the intended purpose through chemical action in or on the body, nor do they undergo biotransformation during their use (33).

Medical device vigilance. Set of methods and observations used to detect adverse incidents during the use of a medical device that may cause harm to the patient, operator, or surrounding environment. Problems, malfunctions, harm, or potential harm from the use of medical devices falls under the term *Adverse incident* (39).

Medication error or medical error. An avoidable incident caused by improper use of a medicine that can cause injury to a patient and occurs while there is the managing of the medicine by health care personnel, patients, or the consumer (37).

Medicine. Any medicinal substance and its associations or combinations used in humans or animals that has properties that can prevent, diagnose, treat, relieve, or cure diseases or ailments or be used to affect bodily functions. Medicinal substances or combinations thereof that can be administered to humans or animals for any of these reasons, even if they are offered without explicit reference to such properties, are also considered medicine products (29).

Medicine interaction. Any interaction between one or more medicines, a medicine and a food, or a medicine and a laboratory test. The first two categories of interactions are important because of the effect they have on the pharmacological activity of the medicine by enhancing or diminishing desirable or adverse effects. The importance of the third category of interaction is related to the change that a certain medicine can produce in laboratory test results that influence their reliability (30).

Medicine-related problems. Health problems (i.e., adverse clinical outcomes) resulting from pharmacotherapy. Such problems occur for several reasons and lead to failure to achieve the therapeutic objective or the onset of undesirable effects (37).

Medicine withdrawal. In assessing the causal relationship, the event improves after the medicine is withdrawn, regardless of the treatment received, and/or the medicine was only administered once (28).

Meta-analysis. A statistical method used widely in modern scientific research and increasingly in clinical pharmacology. Its use is to integrate the individual results obtained in two or, usually, multiple studies on a single subject. Also, used to augment the total statistical power by combining the results of independent or prior research (33).

Monitoring. *This is the* systematic data collection for the use of medicines. It should not be used, as a synonym of medicine surveillance or pharmacovigilance (29).

Multisource medicine. This is the equivalent or alternative pharmaceutical products that may or may not be therapeutic equivalents. Therapeutic equivalents are interchangeable. They can be obtained from multiple suppliers because patents do not protect them or because the patent holder has granted a license to produce or market the medicine to other suppliers (36).

Notifier. This is in relation to any health professional who has suspected a probable adverse medicine reaction and reported it to a pharmacovigilance center (28).

Observational study. An analytic epidemiologic study in which the investigator does not determine the assignment of subjects to each group, but merely records (observes) what occurs in reality. This term used for cohort studies, case-control studies, or cross-sectional studies (29).

Off-label use. In the United States and some other countries, this refers to any use of a medicinal product, not approved by the FDA and, consequently, has not been included in the approved labeling but is recognized according to the authorized opinion of certain well-respected professional groups. Such recommendations are based on prescription patterns and regulations that are reasonable and modern and which contains the knowledge of the medicine, the pertinent literature, and current prescribing practices and use by physicians (33).

Outcome. End result of an adverse medicine reaction (29).

Over-the-counter (OTC) medicine. The delivery or administration does not require medical authorization in this medicine. There may be different categories for these medicines depending on the legislation in each country. Therefore, these medicines, dispensed by pharmacies only or by general commercial establishments. Dispensing or sale without prescription should not be confused with the certification of over-the-counter sale (34).

Package insert. Information about the properties, indications, and precautions for use of a certain medicine, presented separately from the primary medicine container.

PAHO. Pan American Health Organization, WHO regional office for the Americas.

Pharmaceutical substance. Any substance administered to humans for prophylaxis, diagnosis, or treatment of a disease as well as to alter one or more physiological functions (33).

Pharmacoepidemiology. This is the study of the use and effects of medicines in large populations; medicine epidemiology. In addition, the study of the consumption and effects of medicines or medication in the community, including medicine use studies, clinical trials, and pharmacovigilance (33).

Pharmacogenetics. This is the study of any change in pharmacological response due to hereditary causes (29).

Pharmacovigilance. The science and activities related to the detection, evaluation, understanding, and prevention of adverse effects of medicines or any other medicine-related problem. Identification and assessment of the effects of acute and chronic use of pharmacological treatment in the total population or subgroups of patients exposed to specific treatments. There is the suggestion that, strictly speaking, of the distinction drawn between monitoring and pharmacovigilance (33).

Methods used for the identification, quantitative risk assessment, and qualitative clinical assessment of the effects of acute or chronic use of medicines in the total population or specific population subgroups (29).

Pharmacovigilance coordinating center. This is the National Pharmacovigilance Reference Center, usually under the regulatory authority. It is recognized throughout the country as having the clinical and scientific knowledge essential for compiling, classifying, analyzing, and disseminating information on medicine safety. It coordinates the work of local centers, administers the national database, and represents the country at international forums.

Pharmacovigilance database. A computer system that can be used to record reports of suspected adverse reactions, once evaluated and coded, and produce alerts or signals (28).

Placebo. An inert substance such as lactose that is used as a supposed medicine. It has no inherent pharmacological activity but can produce a pharmacological response due to the power of suggestion associated with its administration. In other words, a substance with pharmacological activity (e.g., a vitamin) used for a therapeutic purpose unrelated to its known pharmacological effects (30).

Placebo effect. This is a result of the use or administration of a placebo that may be beneficial or adverse. The placebo effect is also part of the overall effect of an active medicine and, consequently, of any medical treatment attributed to that medicine (29).

***Post hoc ergo propter hoc* fallacy.** A fallacy that involves arriving at a conclusion about causality based on the observation of a clinical change in a patient who has undergone any type of therapeutic intervention. This fallacy has permitted the therapeutic use of many medicines of unproven efficacy prior to introduction of the controlled clinical trial. If the patient improved after administration of the medicine, there was conclusion that the medicine was effective (29).

Prevalence. This usually refers to counting the cases of a disease or trait at a given time in a given population. The phenomenon quantified statistically, while incidence is quantified dynamically (29).

Proprietary medicine. A medicine with a certain composition and information and a specific dosage form and dosage, prepared for immediate medicinal use, available and prepared for dispensing to the public, with a uniform name, packaging, container, and labeling approved for marketing by the regulatory authority (28).

Quality assurance. All systematic programmed actions established to ensure that pharmacovigilance activities, conducted and documented in accordance with good pharmacovigilance practices and the pertinent regulatory requirements (28).

Recently marketed medicine. Any medicine marketed for five years or less (which is not necessarily the same as the period of approval).

Record linkage studies. Studies conducted by compiling information from two or more records (e.g., in different groups of medical records). This can be used to determine the relationship between significant health events occurring in remote time periods and areas (38).

Re-exposure. This is used in assessing the causal relationship, when the reaction or event reappears after administration of the suspect medicine (28).

Reporting (*see also* Yellow card). This is the communication of a suspected adverse medicine reaction to a pharmacovigilance center. These reports are usually made using the adverse reaction reporting forms (yellow card), and seek to maintain data confidentiality at all times (28).

Reporting form (*see* Yellow card).

Risk. This is the probability that an event will cause harm, usually expressed as a percentage or rate (38).

Risk factor. A characteristic that is congenital, hereditary, or due to exposure or lifestyle that is associated with the onset of a disease: social, economic, or biological conditions, behaviors, or environments associated with an increase in susceptibility to a specific disease, poor health, or injury or that cause them (34).

Safety. Characteristic of a medicine used with a very low probability of causing unjustifiable toxic effects. Medicine safety is therefore a relative characteristic and is hard to measure in clinical pharmacology due to the lack of operative definitions and for ethical and legal reasons (33).

Serious adverse reaction. Any lethal reaction can be life threatening, and implies an impairment or disability, which results in hospitalization or prolonged hospital stay, causes a persistent or significant impairment or disability, or is a congenital anomaly or birth defect (28).

Severity of adverse reaction (*see also* Intensity) This can be distinguished as follows:

- **Mild**: Insignificant or minor clinical manifestations that do not require any significant therapeutic measure or justify the suspension of treatment.
- **Moderate**: Significant clinical manifestations that are not an immediate threat to the life of the patient but require therapeutic measures and/or discontinuation of treatment.
- **Severe**: Reactions that cause death are life-threatening, cause permanent or significant disability, require hospitalization or prolong hospital stay, or cause birth defects or malignant processes.

In order to evaluate the severity of an adverse medicine reaction, the intensity and duration of the reaction, as well as the general context in which it occurs, need to be always taken into account (12).

Side effect (*see* "adverse medicine reaction"). This is any unintended effect of a pharmaceutical product that occurs with the normal dosage used in humans and related to the pharmacological properties of the medicine. The essential elements in this definition are the pharmacological nature of the effect, its unintentional nature, and the fact that there is no evident overdose (30).

Secondary effect. An effect that does not occur because of the primary pharmacological action of a medicine but, rather, is an eventual consequence of such action (e.g., diarrhea associated with alteration of the normal bacterial flora balance caused by treatment with antibiotics). Strictly speaking, this term should not be used as a synonym of *side effect* (29).

Signal (*see* Alert)

Source documents. These are original documents, data, and records such as hospital records, medical records, laboratory notes, memoranda, patient diaries, checklists, pharmacy delivery records. Other original

documents include data recorded from automated instruments, copies, or certified transcriptions following verification that they are exact copies, microfiche, photographic negatives, magnetic media or microfilm, x-rays, patient files and records kept at the pharmacy, laboratories, and technical medical departments involved in the clinical trial.

Source documents include all the original documents related to pharmacovigilance reports. This involves reports of telephone conversations or mailed communications from the notifier; internal notes from visiting physicians; suspected adverse reaction; reporting forms (filled out by the notifier or person in charge of pharmacovigilance); results of additional tests or hospital discharges; mailed reports (initial, follow-up, final); or computerized data lists (e.g., news, summaries, tables) related to the report (28).

Spontaneous or voluntary reporting. Information on adverse medicine reactions obtained through voluntary reports from physicians, hospitals, and centers (29).

Spontaneous reporting system. A pharmacovigilance method based on the communication, collection, and assessment of reports of suspected adverse medicine reactions by health care professionals; it also includes adverse clinical outcomes stemming from medicine dependency, medicine abuse, and the incorrect use of medicines (28).

Statistical significance. This is defined as the probability that an observed difference is the result of causality and not of the causal determinants of a study. A finding of statistical significance does not necessarily imply clinical significance (29).

Teratogenicity. Defined as the ability of a medicine to cause harm to the embryo or fetus, and, strictly speaking, structural defects occurring during any stage of its development (29).

Therapeutic ineffectiveness. A medicine-related problem that can occur in several different situations associated with inappropriate use, pharmacokinetic and pharmacodynamic interactions, or genetic polymorphism (28).

Time lapse. In assessing the causal relationship, this is the time between the start of treatment and the onset of the first signs of the reaction (29).

Toxicity. A substance is harmful to this degree. Harmful phenomena caused by a substance or medicine that are observed after administration (33).

Type A effects. Effects caused by (augmented) pharmacological effects. These effects tend to be common, dose-related, and avoided by using doses that are more appropriate for the individual patient. Such effects usually reproduced and studied experimentally and identified before marketing (13).

Type B effects. These effects that typically occur in only a minority of patients and have little or no relationship to the dose. They are usually rare and unpredictable and may be serious and difficult to study. They may be immunologic or not and occur only in patients with predisposing factors, which are often unknown. Immunologic reactions may range from rash, anaphylaxis, vasculitis, or inflammatory organ lesions to highly specific autoimmune syndromes. Nonimmunologic Type B effects also occur in a minority of predisposed patients who are intolerant (e.g., due to a metabolic birth defect or an acquired deficiency in a certain enzyme that results in an abnormal metabolic pathway or the accumulation of a toxic metabolite) (12).

Type C effects. These are situations in which, often for unknown reasons, use of the medicine increases the frequency of “spontaneous” disease. Type C effects (including malignant tumors) may be serious and frequent, and may have a pronounced public health impact. They may be coincidental and related to long-term effects; there is often no suggestive temporal relationship, and the association with the medicine may be hard to prove (12).

Type D effects. These include carcinogenesis and teratogenesis (12).

Unacceptable indication. Any medicine indication considered to be inappropriate, obsolete, or that has not been recommended by the competent authorities or well-known publications (33).

Underreporting. Record of adverse effects that does not reflect the actual patterns of adverse reactions in the population. This is also the main disadvantage of spontaneous reporting of undesirable effects (29).

Undesirable effect. This is a synonym of adverse reaction and adverse effect (29).

Unexpected adverse reaction. A reaction not described in the product labeling or has not been reported to the health authorities by the laboratory that obtained the marketing authorization when it was requested (see

also “adverse medicine reaction”). An adverse reaction of a nature or intensity that is inconsistent with the local information or marketing authorization, or no expectation based on the pharmacological characteristics of the medicine. The predominant element in this case is that the phenomenon is unknown (28).

Uppsala Monitoring Center (UMC). The Uppsala International Center for Medicine Monitoring dependent on WHO (36).

Validated reporting. A validation of a report when the identity of the notifier and/or the origin of the report has been verified (28).

Verification. Procedures required in pharmacovigilance ensuring that the data included in the final report coincide with the original observations. These procedures can be used for the medical record, individual form data, lists, tables, and statistical analysis (28).

Vigimed. This is the name of the e-mail distribution list maintained by the Uppsala International Center for Medicine Monitoring, a WHO agency. It allows pharmacovigilance centers around the world to rapidly share information about medicine-related problems (36).

WHO. World Health Organization.

WHO Adverse Reaction Terminology (WHO-ART). A WHO dictionary containing the terminology for coding clinical information on adverse medicine reactions (40, 41).

Withdrawal syndrome. Onset of a predictable series of signs and symptoms resulting from abnormal activity, primarily in the central nervous system, due to the sudden interruption or rapid reduction of medicine administration (33).

Yellow card. The yellow (also white or light blue) form used to record suspected adverse reactions. The national pharmacovigilance program distributes it to health care professionals for reporting purposes. It collects information about the patient (e.g., identification, age, sex, weight), the suspect medicine (e.g., name, dose, frequency of use, start and end date, therapeutic indication), the adverse reaction (e.g., description, date of onset and resolution, outcome, effect of re-exposure if any), and the professional who sends the report (e.g., name, address, phone number, position, health care level) (28).

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Abbreviations and Acronyms

ADR: Adverse drug reactions

AERS: Adverse Event Reporting System, FDA

ANMAT: Argentine National Administration for Medicines, Food, and Medical Technology

ANVISA: Brazilian National Health Surveillance Agency

EMEA: European Medicines Agency

ESAVI: Events supposedly attributable to vaccination or immunization. Cards used to report vaccine-related adverse events.

FDA: Food and Drug Administration, United States

FEDRA: Spanish Pharmacovigilance System Database of Adverse Reactions

INN: International Nonproprietary Name

INVIMA: Colombian National Institute of Food and Medicine Surveillance

MRA: Medicines Regulatory Autority

PAHO: Pan American Health Organization

PV: Pharmacovigilance

UMC: Uppsala Monitoring Center

VAERS: Vaccine Adverse Event Reporting System. System used to report vaccine-related adverse reactions.

WHO: World Health Organization

WHO-ART: WHO Adverse Reaction Terminology. WHO terminology dictionary for drug-related adverse reactions.

Annex I. Project Evaluation Indicators for Reference Agencies in the Region of the Americas and Guide to their Application.

PHARMACOVIGILANCE		
1. Legal underpinnings	**Response, with the respective support**	**Suggestions**
1.1. There are legal mechanisms governing post-marketing surveillance of the safety of pharmaceutical products		
1.2. Legal mechanisms require the national regulatory authority to set up a surveillance system to compile useful information for pharmacovigilance in order to evaluate this information and make the appropriate decisions.		
1.3. There are legal mechanisms requiring marketing authorization holders to record, collect, and maintain data, evaluate and monitor adverse reactions/events, and report them to the national regulatory authority in specific circumstances.		
1.4. The legal mechanisms require manufacturers, distributors, importers, and exporters to report adverse reactions or events to the marketing authorization holder and the national regulatory authority in specific circumstances.		

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1.5. The legal mechanisms state that health professionals must report adverse reactions or events to marketing authorization holders, the national regulatory authority, or another competent authority.		
1.6. There are specific requirements for reporting safety issues related to specific product categories (vaccines, biologicals, etc.).		
1.7. There are specific requirements that marketing authorization holders, manufacturers, distributors, and wholesalers put a trained individual in charge of monitoring post-marketing safety.		
1.8. There are legal mechanisms defining the terminology used - for example, adverse event, adverse reaction, serious adverse event, etc.		
1.9. Legal mechanisms establish the time frame (delay, frequency, or both) for reporting adverse events.		
1.10. There are specific requirements that health institutions (clinics, hospitals, etc.) designate an individual to be responsible for monitoring post-marketing safety.		
2. Directives and guidelines	**Response, with the respective support**	**Suggestions**
2.1. There are guidelines for monitoring post-marketing safety related to the recording, reporting, and form that should be used.		

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2.2. There are guidelines for the classification of events related to safety.		
2.3. The guidelines for safety reports contribute to scientific evaluation of the benefit/risk ratio of the medicines.		
2.4. There are guidelines defining the scientific knowledge and training that skilled personnel and the focal points in charge of pharmacovigilance should possess.		
2.5. There are guidelines for the criteria to determine the time frames and means for reporting adverse events (severe, expected, etc.).		
3. Organization and structure	**Response, with the respective support**	**Suggestions**
3.1. Surveillance activities in the country are centrally organized and adopted.		
3.2. Activities assigned to other agencies or authorities as part of decentralization are governed by the same standards, guidelines, and procedures.		
3.3. In the case of decentralization, an information exchange mechanism is being adopted and implemented so that the decentralized organization receives requests or directives from the central authority and at the same time can report to it.		
3.4. The mechanisms permit appropriate cooperation and collaboration among decentralized organizations.		

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4. Internal procedures	**Response, with the respective support**	**Suggestions**
4.1. External information (information sources and reference materials) for decision-making on adverse medicine reactions and safety monitoring is readily available.		
4.2. The national regulatory authority has documented procedures for registering and evaluating the daily reports on adverse reactions.		
4.3. The national regulatory authority has documented procedures for analyzing safety trends for the detection of signals.		
4.4. A system has been set up to prioritize safety signals on the basis of their public health impact and to show that high-risk problems are immediately or promptly investigated.		
4.5. An internal monitoring system (which may or may not be established in the legislation) has been set up to monitor whether reporting deadlines are met.		
4.6. Any lack of efficacy due to suspected counterfeit medicines is expected to be found during the evaluation process.		
4.7. There are documented procedures for decision-making and recommending what action the national regulatory authority, manufacturer, or other direct stakeholders should take.		
4.8. The national regulatory authority regularly organizes campaigns to promote pharmacovigilance.		

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4.9. Consumers are involved in the program to monitor safety.		
5. Human and other resources.	**Response, with the respective support**	**Suggestions**
5.1. There are suitable personnel and expertise (education, experience, and training) for safety monitoring activities.		
5.2. Documented quality control measures, such as peer review, have been adopted.		
5.3. External experts participate in the evaluation of the safety information transmitted through the pharmacovigilance network.		
5.4. There is an expert advisory committee that participates in the review of the safety information transmitted through the pharmacovigilance network.		
6. Records and results	**Response, with the respective support**	**Suggestions**
6.1. The safety information collected is used in making or amending regulatory decisions on original marketing permits (adding information, restricting use, removing products, etc.).		
6.2. The national regulatory authority maintains the information/database on reported safety events and the action taken. The terminology recommended by WHO is used.		
6.3. The national regulatory authority maintains a file on each adverse medicine reaction with the supporting documentation.		

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6.4. The database enables the national regulatory authority to evaluate and interpret the safety signals (calculate incidence rate, evaluate causality).		
7. Availability of information	**Response, with the respective support**	**Suggestions**
7.1. The information on adverse medicine reactions and the action taken in terms of safety monitoring are communicated to the public, even the safety alert.		

Indicator Application Guide:

Practical guidance for conducting a review. (Based on the WHO Data Collection Tool for the Review of Medicine Regulatory Systems) Working document adapted to meet the requirements of the PAHO Project on National Regulatory Authorities for Regional Reference. Basic document: *Practical Guidance for Conducting a Review (based on the WHO Data Collection Tool for the Review of Medicine Regulatory Systems).*

Pharmacovigilance

Objectives:

- Evaluate the organizational structure for information gathering
- Evaluate the safety of pharmaceutical products and make the appropriate decisions

The main objective of this annexed guide is to evaluate the surveillance of adverse medicine reactions as indictors of medicine safety. In order to do this, an effective reporting system should be set up. It is recommended that the national regulatory authorities collect, analyze, and evaluate information on reported adverse medicine reactions and make the pertinent decisions.

National governments are responsible for allocating the resources necessary to create their own mechanism for reporting adverse reactions and exercising their regulatory authority to use the information gathered. They will then issue the initial reporting requirements based on their organizational structure, with a view to eventually raising those reporting requirements to the level of a formal reporting process when that structure becomes more sophisticated. Linkage with other international organizations and national regulatory authorities is essential for obtaining, sharing, and exchanging relevant information on medicine safety and deciding on the appropriate action to take.

Linkage with other international organizations and national regulatory authorities is essential for obtaining, sharing, and exchanging relevant information on medicine safety and deciding on the appropriate action to take.

The national regulatory authority or a subagency should offer training programs to promote pharmacovigilance among health professionals.

A. Legal Underpinnings

Evaluators should review the current legal requirements and determine whether appropriate regulations have been issued.

Legislation should include adequate and proportional sanctions, fines, and court proceedings for violations of the legislation in force.

B. Directives

Evaluators should review the guidelines published for the different types of agents and entities involved and determine whether they conform to the current legislation and regulations. When different organizations are involved, the functions and responsibilities of each should be clearly defined. Consistency with PAHO/WHO guidelines should be verified and any differences noted.

C. Organization and Structure

Evaluators should determine the organizational entity that will perform this regulatory function; the characteristics of the function (delegated or decentralized); and, especially, the level at which it operates (central, regional, or local). If different organizations operate at different levels of government, the evaluators should review the linkage among them—in particular, the mechanisms used to set up and administer information exchange.

In order to determine the level of Pharmacovigilance in terms of the indicators for health care systems, evaluators can use the number of contacts in the country and the number of adverse medicine reactions reported.

D. Internal Procedures

Evaluators should review the procedures, bearing in mind the expected results, their level of detail and suitability in terms of the training provided, the steps taken to verify the activities described, and especially, their consistency with current guidelines, regulations, and legislation. In the context of pharmacovigilance, evaluators should pay close attention to delays incurred by manufacturers and the administrative, intermediate, and central levels the time it takes them to transmit, investigate, and evaluate information. They should also examine the extent to which inspection is involved in the monitoring of pharmacovigilance practices and, especially, whether inspections are actually being conducted. The following indicators can be used to gauge the degree to which national regulatory authorities exercise pharmacovigilance:

- Number of facilities inspected for pharmacovigilance purposes during the year in question.
- Average number of days required, per facility, for on-site inspection.

E. Human and Other Resources

The evaluation of human resources should focus on quantitative and qualitative aspects. For quantitative aspects, evaluators can use the following indicators to determine whether suitable human resources are being used to carry out the programmed activities:

- Workload for the functions performed, with the following indicators: number of adverse drug reactions reported and periodic reports reviewed.
- Number of science staff participating.
- Work backlog or delay (workload vs. the number of decisions made).
- Number of investigations conducted.
- Number of warning letters/safety reports issued.
- Average number of days taken by the national regulatory authorities to issue a decision.

Evaluators should determine whether the staff involved in pharmacovigilance are fully competent, especially in the following areas:

- Experimental toxicology.
- Studies in animals.
- *In vitro* tests.

- Clinical pharmacology.
- Pharmacoepidemiology.
- Utilization of medicines.
- Statistics and epidemiology.

If outside experts or an advisory/technical committee participate in this regulatory process, the evaluators should refer to the applicable questions in Chapter 3.8 of the original document, which is not fully reproduced here.

F. Records and Results

Evaluators should determine how the information collected during the data entry and evaluation process is administered and what type of information is entered and stored by the pharmacovigilance agency.

On reviewing the organization's internal procedures, evaluators should sample the files generated and verify their content. Internal objectives, planning, and projected time frames should verified with the evidence reviewed. Evaluators should verify whether the results of this process will be used as input for related procedures such as marketing authorization or regulatory inspection.

G. Availability of Information

Evaluators should review the information that is publicly available and determine whether the media used (website, official bulletin, or another bulletin of the national regulatory authority) are appropriate and whether the information is maintained and updated on a regular basis.

Documentary evidence to be studied

- Regulations, laws, decrees.
- Internal procedures and records.
- Initial and periodic reporting forms for adverse medicine reactions.
- Form for exchanging information with other national regulatory authorities and WHO.
- List of staff and their qualifications.

Bibliography

World Health Organization. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. Why Health Professionals Need to Take Action. Geneva: WHO; 2002.

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World Health Organization. The Safety of Medicines in Public Health Programs: Pharmacovigilance: An Essential Tool. Geneva: WHO; 2006.

Consumer reporting of adverse medicine reactions. (WHO Drug Information. 2000:14(4).

World Health Organization. WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems Geneva: WHO; 2004.

Annex II. Model Spontaneous Reporting Card

Patient data: (to avoid duplication of reports, at least the initials of the first and last names are required)

Name initials		Age		Weight		Height		Sex		Hospitalized (Yes–No)	

Patient data will be handled confidentially in all cases

Brief description of adverse event	

Brief description of patient's clinical symptoms	

Additional relevant tests (with dates)	

Relevant medical conditions	

Medicine(s) (indicate the suspect agent first)

Generic name	Patent name	Daily dosage	Route	Beginning (date)	End (date)	Therapeutic aim	Number of doses received

Outcome:

Recovered	☐	Did discontinuation of the suspect medicine or reduction of the dosage cause the adverse event to fade or disappear?	Yes	No
Recovered with sequelae	☐	Did re-exposure to the medicine cause the same or a similar adverse reaction?		
Did not recover	☐	Date the event began: _____/_____/_____		
Unknown	☐			
Required or prolonged hospitalization	☐			
Birth defect	☐	Date of this report: _____/_____/_____		
Life-threatening	☐			
Lethal (date)	☐			

This information is confidential (it will be used only for subsequent communication with the notifiers)

Name or initials of notifier			
Employer			
Profession		Address	
Tel-Fax		E-mail	
City	Province or state	Zip code	

Instructions for filling out the Pharmacovigilance Card:

Patient name: Initials alone can be used.

Weight: In kilograms. Use two digits for children.

Height: In meters, with two digits. This data is important when the patients are children or when cancer medicines are involved.

Age: In years. If the patients are children under 2 years of age, the age should be stated in months and the date of birth should be added. When a birth defect is involved, indicate the age and sex of the infant at the time it was detected. Add the mother's age.

Sex: Use "F" for female and "M" for male.

Description of clinical symptoms: mention the underlying disease and any important prior medical condition.

Description of adverse event: indicate the signs and symptoms of the adverse episode that led to the report, even if it is a known adverse reaction.

In the case of birth defects, indicate at what point in the pregnancy the medicine in question was administered.

When there is a lack of therapeutic response to a medicine, it should be reported as an adverse event.

In cases of therapeutic failure, it is important to include additional information about the medicine (e.g., patent name, batch number, expiration date)

Medicines: Indicate first the suspect medicine, its generic name (INN), and patent name.

Report all other medicines administered to the patient, including those used for self-medication.

Note: Vaccines, over-the-counter medicines, radioactive medicines, medicinal plants, magisterial formulas, homeopathic medicines, and medicinal gases should be considered medicines.

Indicate the daily dosage. In pediatric patients, the dose should be stated per kg of weight. Indicate the route of administration: oral, intramuscular, intravenous.

Therapeutic aim: Indicate the cause or symptom that led to the use of the medicine.

CONCERNING THE REACTION

Outcome: After the reaction was observed, what was ultimately the result? Mark the different situations with an “X”

Indicate whether re-exposure to the medicine caused the same or a similar adverse reaction.

Adverse effects caused by technology (e.g., catheters) should be reported.

Information about the notifying professional: Initials alone can be used, and the information essential for communicating with him or asking questions, if necessary.

Note: This form represents a model adverse event reporting form. The idea is not to attempt to impose a universal model, but to indicate the basic information that should be included in the report.

Annex III. Naranjo *et al.* Algorithm and Food and Drug Administration (FDA) Causality Algorithm

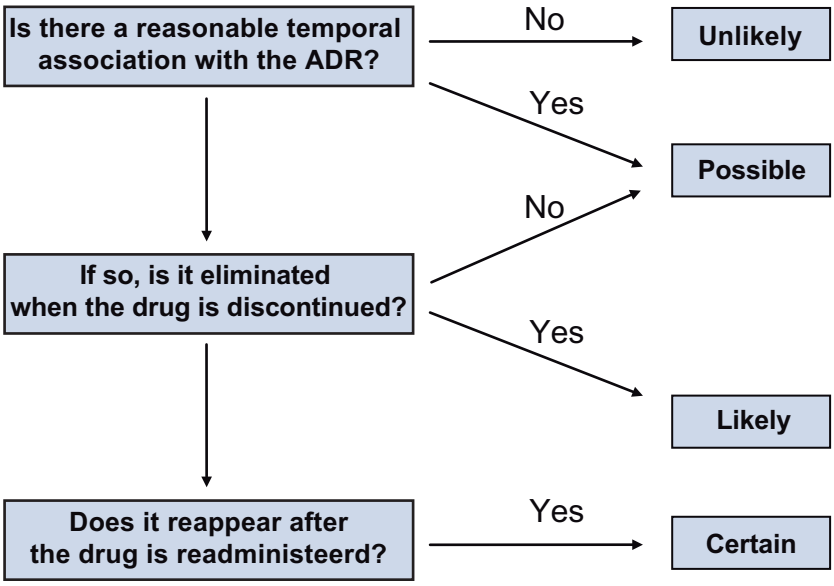
Naranjo Algorithm

	Yes	No	Unknown	Points
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse reaction occur after the suspected medicine was given?	+2	-1	0	
3. Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was given?	+1	0	0	
4. Did the adverse reaction reappear when the medicine was readministered?	+2	-1	0	
5. Are there alternative causes (other than the medicine) that could have caused the reaction?	-1	+2	0	
6. Did the adverse reaction reappear when a placebo was given?	-1	+1	0	
7. Was the medicine detected in any bodily fluid in toxic concentrations?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE				

Source: Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Phamacol Ther. 1981; 30:239-45.

Scoring: Certain: ≥ 9 points. Likely: 5-8 points Possible: 1-4 points Unlikely: ≤ 0

FDA Causality Algorithm



Annex IV. Summary of Responsibilities in Pharmacovigilance

Patients, public	Comply with the treatment prescribed and report adverse events to the health professionals and other health worker with whom they come in contact.
Health care professionals	Diagnose the adverse events. Manage the adverse events. Refer patients with serious and very serious adverse events to the main hospitals for management and investigation. Perform a basic causality assessment. Report any suspected serious or unexpected medicine-related adverse reactions or problems. Send such information as soon as possible to the appropriate local or national center, using the yellow card. Keep clinical documentation on adverse medicine reactions Cooperate with the technical heads of the national pharmacovigilance system. Stay informed about safety data related to medicines that are customarily prescribed, dispensed, or administered. Educate patients. Prevent errors. Promote rational medicine use. Follow treatment guides. Communicate with patients and the public. Attend meetings in order to receive information from the appropriate pharmacovigilance center. Take the action indicated by the local pharmacovigilance center
Hospitals and other inpatient	Distribute the reporting forms to all hospital health care professionals. Receive, assess, and process the reports on suspected adverse reactions sent by hospital professionals. With the notifier, complete any required information not initially available. Identify the valid reports and send them to the coordinating center. Send information about serious or fatal cases in the hospital to the coordinating center within 24 hours. Maintain the confidentiality of personal information on patients and notifiers. Review and purge the reports received to prevent duplication. Perform an in-depth study and review the available scientific literature. Propose and develop pharmacoepidemiologic studies in your hospital to evaluate the medicine safety profile Respond to requests by hospital professionals for information on adverse reactions. Promote training programs in hospital pharmacovigilance and pharmacoepidemiology for health professionals and technical staff and actively participate in them. Respect the standards and procedures established by the country's national health authority. Give feedback to notifiers.

Local pharmacovigilance centers	Lead the pharmacovigilance team in your region. Implement, develop, and strengthen reporting in your geographical area. Receive, assess, and process reports from your geographical area. Send reports on suspected serious adverse reactions to the coordinating center of the national pharmacovigilance system within 10 calendar days. Print and distribute reporting cards. Document and validate reporting data, verifying its authenticity and consistency with the originals. Maintain the reliability of the data reported. Maintain the confidentiality of the personal information on patients and notifiers. Provide a timely and appropriate response to reports from professionals to encourage participation. Archive all reports. Develop methods for obtaining early signals or alerts. Contribute to scientific progress. Respond to requests for information by health professionals and authorities. Promote and participate in training for health professionals. Participate in the meetings of the national pharmacovigilance system. Establish a quality assurance system that ensures good pharmacovigilance practices. Coordinate and complete the investigation of adverse events. Report adverse events and follow-up details to the coordinating center and the appropriate person in the national pharmacovigilance system. Assess the causal relationship Make decisions about medicines at the local level. Make decisions as advised by the expert safety committee. Train and supervise local health teams and centers.
National pharmacovigilance center	Act as the pharmacovigilance reference center. Receive, assess, code, and upload to the database the reports sent by the pharmaceutical laboratories. Guarantee the safety and confidentiality of the data, as well as its integrity during data transfer processes. Coordinate the activities of peripheral centers. Verify that all reports of serious suspected adverse reactions occurring in the national territory are entered and communicated as soon as possible. Manage the national pharmacovigilance system database. Guarantee the quality of the database. Develop methods for obtaining early signs and alerts. Coordinate the monitoring of publications on adverse reactions. Ensure that the data from the reports collected comply with good pharmacovigilance practices. Establish contact with national pharmacovigilance centers in other countries. Act as the national reference center for the WHO international pharmacovigilance system Inform the therapeutic committees and all competent agencies about urgent measures adopted with respect to safety issues. Conduct medicine safety studies. Promote information and training in pharmacovigilance at all national health centers. Send the results of the reports to the notifiers (health care professionals), since they are the backbone of the reporting system.

Expert Committee	Evaluate the benefit/risk ratio of medicines and issue recommendations when necessary. Propose studies and research on pharmacovigilance Collaborate in the coordination, planning, and development of the pharmacovigilance system when evaluating post-marketing studies. Provide technical assistance.
Pharmaceutical laboratory	Report all serious suspected adverse reactions received from health care professionals Keep a detailed record of all suspected adverse reactions Designate a qualified professional to be responsible full-time for pharmacovigilance tasks. Propose changes in the data sheet, labeling, and package insert Ensure that there is a filing system for storing the documents. Establish an audit program
National Regulatory Authority	Develop national policies and action plans. Create a national pharmacovigilance system. Designate and/or create an official coordinating center. Report and manage suspected adverse reactions. Prepare and/or review periodic safety reports. Continuously assess the benefit/risk ratio during the post-marketing period. Set criteria to identify and assess the severity of signals or alerts. Supervise post-marketing safety studies. Periodically review the scientific literature on spontaneous adverse reactions to authorized medicines. Cooperate with pharmacovigilance centers in medicine safety studies. Verify that the pharmaceutical laboratories have medicine monitoring programs Monitor the pharmacovigilance activities of pharmaceutical laboratories. Inspect pharmaceutical laboratories' compliance with good pharmacovigilance practices.

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Good Pharmacovigilance Practices for the Americas