



**PAN AMERICAN NETWORK ON DRUG REGULATORY
HARMONIZATION**

WORKING GROUP ON PHARMACOVIGILANCE

November, 2008



GOOD PHARMACOVIGILANCE PRACTICES FOR THE AMERICAS

Public Opinion Document

2008

Pharmacovigilance Group of the Pan American Network for Drug Regulatory Harmonization (PANDRH) of
the Pan American Health Organization (PAHO)

CONTENTS

1. FOREWORD	5
2. DOCUMENT OBJECTIVES	6
2.1. Document Structure	7
3. INTRODUCTION	7
4. GOOD PHARMACOVIGILANCE PRACTICES	13
4.1. General Principles	13
4.2. Organization of National Pharmacovigilance Systems and Centers	14
4.2.1. Basic Activities in Setting up a Pharmacovigilance Center	15
4.2.2. Financial Resources	16
4.2.3. Locale	17
4.2.4. Necessary Equipment	17
4.2.5. Staff	18
4.2.6. Continuity of the Service	18
4.2.7. Advisory Committees	19
4.2.8. Information Service	19
4.3. Documentation	19
4.3.1. Characteristics of Reporting	20
4.3.2. Other Documents	23
4.3.2.1. Manuals	24
4.3.2.2. Procedures	24
4.3.2.3. Additional Documentation	25
4.4. Computer Systems	26
4.5. Management of the Reports	26
4.5.1. Methods for Sending Reports	27
4.5.2. How to Improve Reporting	28
4.5.3. Data Coding and Recording	28
4.5.4. Inspection of the Database	29
4.5.5. Report Evaluation	30
4.5.5.1. Severity of the Reaction	31
4.5.5.2. Chronological Sequence	32
4.5.5.3. Causality or Imputability Relationship	32
4.5.5.4. Mechanism of Adverse Reactions	34
5. GOOD RISK ANALYSIS AND MANAGEMENT PRACTICES	35
5.1. Identification of Risks	37
5.1.1. Descriptive Analysis of a Series of Cases	37
5.1.2. Use of Data Mining	39
5.2. Generation of Signals	41
5.3. Quantification of Risks	41

5.3.1. Studies to Quantify Risks	42
5.4. Risk Assessment	44
5.4.1. Assessment of the Benefit/Risk Ratio	44
5.5. Risk Management	44
5.5.1. Risk Minimization Plan	45
5.5.2. Administrative Measures for Risk Reduction	46
5.6. Risk Communication	49
5.6.1. Periodic Safety Updates	49
5.6.2. Crisis Management	50
5.7. Risk Prevention	51
5.8. Evaluation of the Pharmacovigilance System	51
6. DUTIES AND RESPONSIBILITIES OF AGENTS INVOLVED	52
6.1. National Regulatory Authority	54
6.2. National Pharmacovigilance System	56
6.2.1. National Pharmacovigilance Centers	57
6.2.2. Local Pharmacovigilance Centers	58
6.3. Health Professionals	59
6.4. Pharmaceutical Laboratory or Licensed Manufacturer	60
6.5. Other Health Institutions	61
6.5.1. Hospitals and Other In-patient Centers	61
6.5.2. Universities	62
6.5.3. Drug and Toxicology Information Centers	63
6.5.4. Safety Committee on Drugs for Human Consumption	63
6.5.5. Professional Associations of Physicians and Pharmacists	64
6.5.6. Consumer Organizations and the Media	64
7. PHARMACOVIGILANCE PUBLICATIONS	64
7.1. Publisher Participation	65
7.2. Guidelines for Editors and Authors to Consider when Publishing Information on Adverse Reactions	66
7.3. Publications on Series of Multiple Cases	67
8. GLOSSARY OF TERMS USED IN PHARMACOVIGILANCE	68
9. ACRONYMS	86
10. ANNEX I Model Spontaneous Reporting Card	87
11. ANNEX II Algorithm of Naranjo et al. and FDA Causality Algorithm	89
12. ANNEX III Summary of Responsibilities	91

1. FOREWORD

Drug toxicity is an issue of particular concern among patients, prescribers, dispensers, and regulatory authorities: Adverse reactions are a major cause not only of medical consultation but of hospital admissions and, at times, of patient deaths. Moreover, in recent years, many drugs have been withdrawn from the market as a result of an unfavorable benefit/risk ratio that had not been detected when their sale was authorized.

As described in the report of the WHO World Alliance for Patient Safety,¹ one of the main elements of programs to improve patient safety is the capacity and quality to obtain the most complete information possible on adverse reactions and medication errors, so that it can be used as a source of knowledge and the basis for future preventive action. If no action follows an event or the findings of any study, the lesson usually cannot be learned, the opportunity to generalize the problem is missed, and the capacity to develop broader, powerful, and applicable solutions will not be manifested^{Error! Bookmark not defined.}. Two elements are fundamental: (1) adequate training in clinical and therapeutic pharmacology at all levels to achieve better use of drugs, and (2) a pharmacovigilance system.

Health needs and drug usage vary considerably from country to country. There are many reasons for this, such as the burden of disease, economics, ethnicity, culture, and diet, as well the level of development and drug regulatory system. Decisions concerning safety and effectiveness must be considered in the specific context of each country. Therefore, monitoring the safety and effectiveness of drugs must be a public health priority.

Generally speaking, pharmacovigilance systems are imperfect. Pharmacovigilance in Latin America and the Caribbean is still deficient; it suffers from the same shortcomings as in the developed countries: underreporting, reports of already-known adverse effects, conflicts of interest deriving from prescribers' and dispensers' links to the pharmaceutical industry, lack of motivation to report among health professionals. However, these deficiencies are compounded by others: health systems that are inequitable and individualistic rather than collective; a high percentage of population with no access to the health system or medical care; patients who have little direct interaction with health professionals, which fosters the use of "home remedies" based on medicinal herbs that do not go through the manufacturing process and are not subject to any controls. Other deficiencies are the presence of combination drugs on the market in irrational fixed doses, whose efficacy has not been demonstrated; the use of drugs for off-label indications, not to mention greater problems, such as the ability to purchase drugs like antibiotics without a prescription, Internet sales of drugs, etc.

¹ WORLD ALLIANCE FOR PATIENT SAFETY WHO Draft Guidelines for Adverse Event Reporting and Learning Systems: From Information to Action 2005 EIP/SPO.

Within this context, pharmacovigilance in the 21st century is an issue that must be addressed. Thus, it is very important to ensure its harmonization in the Region of the Americas and to develop guides for good pharmacovigilance and risk management practices. Active pharmacoepidemiology-based pharmacovigilance programs must be created, since the planning of activities prior to the approval of the drugs will benefit public health in the Region.

PAHO/WHO is interested in developing good practices guides that can be used to facilitate and improve the pharmacovigilance reporting system to improve patient safety. The central principles in the development of this guide are that:

- The main role of reporting systems for improving patient safety is to learn from failures.
- Reporting should be safe; people who report incidents should not be punished or suffer other consequences.
- Reporting is valuable only if it results in a constructive response.

At a minimum, this process results in feedback from the findings of the data analysis. Ideally, it also produces recommendations for changes in health processes and health systems: significant analysis, learning from the reports, and disseminating what has been learned demands expertise and other human and financial resources. The authority who receives the reports must be able to influence solutions, disseminate the information, and make recommendations for change².

2. DOCUMENT OBJECTIVES

The Pharmacovigilance Group of the Pan American Network for Drug Regulatory Harmonization (PANDRH) of the Pan American Health Organization (PAHO) has based this document on the PAHO/WHO vision, considering pharmacovigilance an essential component of public health programs.³ Its objective has been to facilitate development, improve and strengthen pharmacovigilance systems in the Region of the Americas, and encourage the use of good practices to improve patient and population safety based on the Region's needs.

This document offers guidelines to answer two questions:

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

² Generalidades acerca de la Farmacovigilancia. *Dr. Leobardo Manuel Gómez-Oliván y Dra. Araceli Amaya Chávez*. Departamento de Farmacia de la Facultad de Química de la Universidad Autónoma del Estado de México. At<http://www.infarmate.org/pdfs/Septiembre_octubre/farmacovig_num3.pdf> [acceso septiembre de 2008]

³ *The Safety of Medicines In Public Health Programmes: Pharmacovigilance an essential tool* WHO 2006.

These recommendations are based on WHO documents aimed at promoting and intensifying not only the system for the spontaneous reporting of adverse events, but also active pharmacovigilance studies on drugs in the Latin America and Caribbean region. Countries can select, adapt, or modify the recommendations, as needed. This guide is not a set of international regulations and may be modified to suit experiences and needs in each case.

2.1. Document Structure

The document is divided into numbered sections. Section 3 contains a brief description of pharmacovigilance in the context of drug usage. Section 4 is devoted specifically to good pharmacovigilance practices, describing how to set up a center, from materials to operations. Section 5 describes good practices in analyzing, managing, and communicating the risks identified by the system. Section 6 describes the duties and responsibilities of the agents involved in pharmacovigilance. The next sections contain terminological information, generic reporting cards, and guidelines for analyzing reports, such as causality algorithms and other useful elements for work in this area.

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

3. INTRODUCTION

Modern drugs have changed the way we treat disease or altered health status. However, in spite of all their advantages, there is growing evidence that adverse drug reactions are frequently an often preventable cause of disease, disability, or even death. Adverse reactions are estimated to be the fourth to sixth leading cause of death in some countries^{3, 4, 5}.

Approval of a drug for sale implies that its efficacy has been demonstrated and that any undesirable effects encountered during the premarketing tests were acceptable, **although this does not mean that the benefit/risk ratio is definitive**. Once on the market, the drug leaves the secure and protected scientific medium of clinical trials to become a legal product for public consumption. What most commonly occurs is that, up to its release on the market, the short-term efficacy and safety of the drug have been tested in only a few carefully selected people. The information obtained in the clinical trials, from the different phases up to its approval by the health authority, is not enough to predict what will happen in daily clinical practice in terms of infrequent or slow-to-develop adverse reactions, which are most likely to be detected in the post-marketing phase. At times, as few as 500 people have received the drug before it is released on the market, and the number rarely exceeds 5,000. For this reason, it is essential to monitor the safety and

⁴ *Perspectivas políticas de la OMS sobre medicamentos, boletín 9. La farmacovigilancia: garantía de seguridad en el uso de los medicamentos* October 2004 World Health Organization, Geneva WHO/EDM/2004.).

⁵ Organización Mundial de la Salud. AIDE MEMOIRE.2008 Por una estrategia nacional que garantice medicamentos seguros y su uso apropiado

efficacy of new treatments that are still relatively untested from the medical standpoint, once they are sold under real conditions.

Generally, more information is needed on the use of the drug in specific population groups, especially children, pregnant women, and the elderly. For example, it is critical to detect side effects that are serious, rare, or occur only in the pediatric age group, and also to ascertain a product's safety and efficacy after a lengthy period of uninterrupted use, especially in combination with other drugs. Experience shows that many adverse effects, interactions with food or other drugs, and risk factors do not appear until years after a drug is marketed.

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

PHARMACOVIGILANCE

The Pharmacovigilance is the science and activities related to the detection, evaluation, understanding, and prevention of the adverse effects of drugs or any other problem linked with them.

Its goals are:

- To improve patient care and safety in relation to the use of medicines and all medical interventions.
- To improve public health and safety in relation to the use of drugs.
- To detect problems linked with the use of drugs and communicate the findings in a timely manner.
- To contribute to an assessment of the benefits, threats, effectiveness, and risks of drugs, with a view to preventing threats and maximizing benefits.
- To promote the safe, rational, and more effective use of drugs (including cost-effectiveness).
- To promote an understanding of and education and clinical training in pharmacovigilance and its effective communication to the public.

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

Here it is important to define the term **Adverse Drug Reaction (ADR)**, which, according to WHO, is “a response to a drug that is noxious and unintended and occurs in doses normally used in man for the prophylaxis, diagnosis, or therapy of a disease, or for modification of physiological function.” This definition

implies a causal relationship between the administration of the drug and the appearance of the reaction. Today, the preferred definition is “undesirable effect attributable to the administration of...” reserving the original definition of WHO for the concept of *adverse event*, which does not necessarily imply the establishment of a cause-and-effect relationship.

Pharmacovigilance is concerned with the undesirable effects or ADRs produced mainly, but not exclusively, by drugs, since its sphere has been expanded to herbs, complementary drugs, blood products and biologicals, vaccines, medical devices, medication errors, lack of efficacy, and other areas ⁶.

Pharmacovigilance is also concerned with the use of drugs for indications that have not been approved and for which adequate scientific evidence is lacking, the use of substandard drugs, the reporting of cases of acute and chronic poisoning, studies of drug-related mortality, the abuse and misuse of drugs, and drug interactions with other chemicals, medicines, foods, and beverages.

Furthermore, in recent years the media—the press, television, Internet—have fostered medicalization, encouraging the use of drugs for minor symptoms or simply to get healthier. All of this increases the number of adverse reactions, which can result in death or disability and prolong a hospital stay, constituting the highest percentage of preventable and avoidable incidents of this type.

Factors such as nutrition and eating habits in a community may have consequences for the therapeutic effectiveness and safety of drugs. Without a good guide and pharmacovigilance training for health professionals in our countries, patients may be at higher risk for preventable medication errors and/or adverse reactions.

Combating risks from the use of drugs calls for close and effective collaboration among the principal entities working in this field. Success and the future will depend above all on permanent willingness to collaborate. Those responsible in this field must engage in concerted action to anticipate, describe, and meet the demands and expectations of the public, health administrators, planners, politicians, and health professionals. However, sound integrated mechanisms to permit this collaboration are lacking. The main stumbling block is usually the lack of professional education, resources, political support, and especially, science infrastructure. Understanding and tackling these problems is essential and a prerequisite for future scientific development and pharmacovigilance ⁴. It is clear that the Latin American and Caribbean countries must be prepared for there to be progress in the new pharmacovigilance.

The pharmacovigilance model adopted must be robust and flexible, as it will not always be used in countries with public health and pharmacovigilance systems in place, but rather in countries with weak and deficient programs. The model must emphasize the sharing of human resources and the dissemination of knowledge about the effectiveness/risk, collaboration, effective communication, integration, training, and capacity building.

Methodology

There are several methods for implementing pharmacovigilance activities ²:

a) Spontaneous reporting system: This involves the identification of suspected adverse drug reactions by health professionals in their daily practice and the forwarding of the information to an agency that centralizes it. This is the methodology used by the pharmacovigilance centers of WHO's International Program for Pharmacovigilance.

b) Intensive pharmacovigilance systems: These are based on the systematic detailed collection of data on all harmful effects thought to be drug-induced in well-defined population groups. They are divided into two major groups:

- Drug-centered systems.
- Patient-centered systems.

c) Epidemiologic studies: The purpose of these studies is to confirm a hypothesis--that is, to establish causality between the presence of adverse drug reactions and the use of a drug. They may be:

- Cohort studies.
- Case-control studies.

The most widespread of the pharmacovigilance study methodologies 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 warnings about the behavior of drugs in the population of our region ⁶. The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse drug reactions.

History and International Context

As a result of the phocomelia epidemic in newborns caused by thalidomide in Europe beginning in 1960, several countries began to "monitor" drugs. In 1968, within the framework of its Program for International Pharmacovigilance the World Health Organization proposed the creation of a center for international pharmacovigilance. This center is currently located in Uppsala, Sweden (Uppsala Monitoring Center, or UMC). A total of 86 active member countries participate in the WHO Program for International Pharmacovigilance; the newest members are Kazakhstan and Barbados, which joined in July 2008.

In the Region of the Americas, Latin America and the Caribbean are making efforts to document adverse events linked with drugs, but this is a relatively recent phenomenon. Since the 1990s, 12 countries have created pharmacovigilance systems through their regulatory agencies and have been recognized as member countries of the WHO Center for International Pharmacovigilance. While not officially members as

⁶ CAPITULO 13: FARMACOVIGILANCIA Y MECANISMOS DE REACCIONES ADVERSAS A MEDICAMENTOS. Mabel Valsecia. http://med.unne.edu.ar/catedras/farmacologia/temas_farma/volumen5/13_farmacovigi.pdf.

yet, the other countries are in the process of developing pharmacovigilance⁷. They are considered associate members by WHO until their formal recognition as centers for the monitoring of adverse reactions.

There are several notification systems around the world, whose nature, scope and complexity vary. A 2002 study compared the characteristics of different spontaneous reporting systems by surveying the regulatory agencies of the 18 countries that participate in WHO's Program for International Pharmacovigilance; 12 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 respond⁸.

Some of the different characteristics of the reporting systems are described below. Reporting by health professionals is voluntary in the all countries except Spain and France, where it is compulsory. Some countries have a decentralized system: France has 21 regional centers, and Spain 17 autonomous centers, with one coordinating center. The system is only partially decentralized in Canada and the United Kingdom. The remaining countries have a single regional center. The reporting program in one country also includes the reporting of adverse reactions to products other than drugs for human consumption. Thus, veterinary drugs are included in Denmark and medical devices, in the United States. In addition, some countries have systems for monitoring the undesirable effects of vaccines that are independent of the program for adverse drug reactions. Some countries have recently developed systems for monitoring specific products such as antiretroviral, antimalarial, and anthelmintic drugs. Pharmacovigilance programs for antiretrovirals in the developing countries, based on cohort studies, are a good example of active pharmacovigilance⁹ that should be imitated and expanded.

General Information on the Reporting System

The most important objective of pharmacovigilance is the identification of adverse events connected with drugs. Clinical observation and **reporting** of suspected adverse reactions are usually the fastest and most effective methods for triggering alerts or causality hypotheses or "signs," and also for designing specific active pharmacovigilance studies that will show the safety profile of the drugs when used in the general population or special populations.

For any of the pharmacovigilance systems to be effective, all health professionals in contact with patients who use the drugs must be involved in the reporting, even though all of this information should be

⁷ The UPPSALA Monitoring Centre. Who Collaborating Centre for International Pharmacovigilance.

⁸ Hughes,ML; Whittlesea,CMC; Luscombe,DK. Review of national spontaneous reporting schemes: strengths and weaknesses. *Adverse Drug React Toxicol Rev.* 2002; 21: 231-241.

⁹ Pharmacovigilance for antiretrovirals in resource-poor countries WHO/PSM/QSM/2007.3.

centralized by a dedicated agency and validated by the health authority, so that it can be disseminated to the community.

The objective is greater safety in the use of drugs through rapid detection of serious adverse reactions, especially with newer drugs, determining the rate of occurrence of adverse effects, predisposing factors, causal relationship, and drug interactions, and studying special population groups (children, pregnant women, patients with renal and liver failure, patients with AIDS). Another objective is to develop training and information programs that encourage active participation by health workers.

The main purpose of a reporting system is to learn from experience. Reporting for reporting's sake does not improve safety; it is the response to the reports that leads to change. The important thing is for a pharmacovigilance system to produce a useful, visible response by the recipient of the report, not only to justify the resources spent on reporting but to encourage individuals and institutions to report. Reporting leads in different ways to learning and improved safety, triggering alerts, disseminating information on experiences, analyzing risk trends, and improving system operations.

The pharmacovigilance systems of Latin America and the Caribbean will have to be more proactive than reactive in the face of alerts and/or withdrawals of drugs from the market; they must develop cooperation mechanisms for capacity building and increase the potential to operate as a Latin American pharmacovigilance network¹⁰. However, any effort will be in vain if it is not accompanied by wide action to strengthen the clinical and therapeutic rationale for using a drug..

4. GOOD PHARMACOVIGILANCE PRACTICES

4.1. GENERAL PRINCIPLES

Good pharmacovigilance practices are a set of rules, operating procedures, and established practices that must be followed to ensure the quality and integrity of the data produced in specific types of research or studies. Good pharmacovigilance practices are based on the procurement of complete data from the spontaneous reporting 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 drugs.
- Confidentiality about the identity of the people who have experienced or reported adverse reactions.
- Use of uniform criteria to evaluate reports and issue signals and alerts.

¹⁰ Boletín de Farmacovigilancia, September-November 2006 INVIMA.

Since effective pharmacovigilance depends on input from many people with very different training, to create a coherent pharmacovigilance system it is important to develop guides with standard operating procedures (see 4.3.2.3 Procedures) describing the practical details of information flows¹¹. These guides should clearly state and standardize the information on:

- What constitutes a reportable adverse event?
- Who is expected to report observance of a suspected drug-related problem?
- The availability and practice of completing reporting forms or yellow cards.
- Procedures for sending or collecting reports.
- Routines for evaluating, monitoring, and processing case reports in pharmacovigilance centers.
- Procedure for analyzing aggregate data and options for action.
- Good communication practices.
- A description of indicators for measuring progress in the monitoring system.

In order to comply with these good pharmacovigilance practices:

- Reports of suspected adverse reactions or problems related to drugs should be recorded, adhering to the principle of veracity in the data provided.
- All reports where the severity or novelty of the suspected adverse reaction warrants it should be thoroughly documented.
- The information on any suspected adverse reaction or problem related to drugs should be verifiable, confirming its authenticity and consistency with the original documents whenever possible.
- The confidentiality of entries that could identify subjects should be protected, respecting privacy and confidentiality rules.
- Information should be processed in a manner that maintains the reliability of the data, using words as similar as possible to those used by the reporter.
- The time frames established for communicating serious suspected adverse reactions should be scrupulously respected, giving them the highest priority.
- Each individual involved in assessing an adverse reaction must be qualified for the task, through education, training, and experience.
- All information that has not yet been validated should be viewed with caution.
- All information on adverse reactions should be recorded, processed, and stored so that it can be communicated, verified, and accurately interpreted.

¹¹ Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) March 2005 Clinical Medical.

- Prior to communicating an adverse reaction to the scientific community, the National Pharmacovigilance Program should be notified.
- Systems and procedures should 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 will in no case be used to make value judgments about the medical action.

4.2. Setting up National Pharmacovigilance Systems and Centers

In order to set up a reporting system for adverse reactions, certain simple or complex capacities are needed. It is essential to clearly define: *objectives; who is responsible for reporting; how to obtain the reports; mechanisms for receiving them and handling data; expert analysis; the capacity to respond to the reports; a methodology for classifying reported events; the capacity to disseminate findings; technical infrastructure; and data security.*

To start a center, the following are needed:

Publicity: It should be recalled that when a national center gets started, 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 linked with drug regulation. Government resources are needed for national coordination.

Collaboration, coordination, communication, and public relations: In order to ensure coherent development and prevent unnecessary competitions or duplication of efforts, good collaboration, coordination, communication, and public relations are necessary.

4.2.1 Basic Activities for Setting up a Pharmacovigilance Center

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

A plan must be drawn up for a pharmacovigilance system (!!!). It should involve:

¹² VIGILANCIA DE LA SEGURIDAD *de los* MEDICAMENTOS Guía para la instalación y puesta en funcionamiento de un Centro de Farmacovigilancia. Published by the Uppsala Monitoring Centre (UMC), WHO Collaborating Centre for International Pharmacovigilance 2002

- Making contact with the health authorities and local, regional, or national institutions and groups working in clinical medicine, pharmacology, and toxicology, stressing the importance of the project and its purposes.
- Setting up the center: office, technical staff, sites, telephones, text processors, capacity in database management, bibliography, etc.
- Designing a reporting form (sample form in Annex I) and beginning to collect data by distributing the form to hospitals, clinics, family doctors in primary health care, pharmacies.
- Preparing printed materials to inform health professionals about the definitions, objectives, and methods of the pharmacovigilance system.
- Training pharmacovigilance personnel in:
 - a. data collection and verification
 - b. interpretation and coding of descriptions of adverse reactions
 - c. coding of drugs
 - d. assessment of causal relation
 - e. detection of signs
 - f. risk management
- 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 drug reactions in medical journals and other professional publications.

4.2.2 Financial Resources

A pharmacovigilance center should have a **basic, regular source of funding (!!!)** to ensure the continuity of its work. The costs are mainly for staff, training, communication, computers and software, and the printing of promotional literature and reporting cards.

These resources can be obtained through registration fees or taxes or through a special compulsory pharmacovigilance fee ¹². Both can be included in the budget of the drug regulatory authority.

In addition to basic resources, the center can seek 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 drug safety
- . Health insurance companies and health insurance funds
- . University departments
- . Professional associations

Because of the significant public health and trade consequences of adverse reactions, the continuity of financial resources for pharmacovigilance should be guaranteed and not be exposed to the potential influence of pressure groups, political change, or economic factors.

The financial resources necessary for pharmacovigilance can be estimated, basing the calculations on the required reporting rate and the size of the population¹². Quantitative and qualitative data collection, along with careful evaluation and distribution of the information, entails costs.

4.2.3 Locale

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

A government department (health authority, national drug regulatory agency) can be a good place for a pharmacovigilance center. Nevertheless, as the initial environment for the development of pharmacovigilance, any department in a hospital or university that works in the area of clinical pharmacology, clinical pharmacy, clinical toxicology, or epidemiology can be used. Reporting of adverse drug reactions can begin locally, perhaps in a hospital, and later be extended to other hospitals and health centers in the Region, moving step by step to the national level. In some countries, professional associations such as national medical associations are used as the location for the center.

4.2.4 Necessary Equipment

The technical infrastructure required can be very simple. For communication, at the very least a telephone, mailing address, or fax are needed to receive the reports. Web-based systems are easy to use for reporting and also reduce the need for personnel to input the data.

The equipment consists of:

- Multi-line telephone (!!!).
- Computers with the capacity (hardware and software) to meet the center's needs (database, text processor) (!!!).
- Printer (!!!).
- Fax (!!!).
- E-mail (!!!).
- Photocopier (!!).
- Website (!!).
- Access to specialized databases procured on the basis of a selection plan and needs (!!).

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

4.2.5 Staff

Work in a pharmacovigilance center requires knowledge in the following areas: clinical medicine, pharmacology, toxicology, and epidemiology. The competencies for assessing case reports on adverse reactions can be acquired through training for center staff and the ongoing use of expert consultants.

Sometimes, however, a new pharmacovigilance center begins operations with only one part-time expert (!!!), normally a pharmacist or doctor, and some administrative support. Soon afterwards, it may be necessary to appoint an expert to be in charge of pharmacovigilance most of the time and to expand the work of the secretariat.

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

Ideally, a National Coordinating Center needs at least (!!):

- A pharmacist, doctor, or a pharmacoepidemiologist.
- Administrative personnel.
- An on-demand programmer or systems analyst.
- An on-demand data processor.
- On-demand experts or consultants.
- New health sector professionals that start in the center as apprentices.

Pharmacovigilance centers or units should prepare an organizational chart clearly indicating posts and their place in the organizational structure, so that the responsibilities and tasks of the team personnel who work there can be defined. This why it is advisable to organize staff according to:

- The center's organizational chart, where posts and their place in the organizational structure are defined (!!!).
- Job description, indicating the basic functions, duties, and responsibilities and their place in the organizational structure (!!).
- Technical pharmacovigilance staff who work in centers should have the qualifications (!!!) established in the standards set for the pharmacovigilance system. This is reflected in their *résumés*.
- Written instructions for each job (!!).
- Initial and ongoing training in good pharmacovigilance practices, as well as quality assurance procedures (!!!).

4.2.6 Continuity of the Service

Continuity of **access and service (!!!)** is basic to the success of a pharmacovigilance center. Consequently, the center needs a permanent secretariat to handle phone calls 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 **6.5.2.**).

4.2.7 Advisory Committees

It is both advisable and desirable for the center to have a multidisciplinary advisory committee **(!!)** to support it, as well as technical assistance in other disciplines and for the quality of procedures in:

- Data collection and evaluation
- Data interpretation
- Publication of the information

An advisory committee can be made up of people from the following disciplines: general medicine, clinical pharmacology, toxicology, epidemiology, pathology, drug regulation and quality assurance, information on drugs, phytotherapy, vaccines, etc.

In addition, it is very useful to have a network of experts in the different specialties. If the center is located in a hospital, it is easier to obtain specialized advisory services. (See **6.5.4 Committee on the Safety of Drugs for Human Consumption**).

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 literature for reference.

Locating the center in a hospital may offer the advantage of access to a library. National pharmacovigilance centers can enjoy direct (online) access to the UMC database. Furthermore, the bulletins on drugs and adverse reactions published by the World Health Organization (WHO) and a number of national or regional centers throughout the world can be in the mailing directory.

Feedback on what has been learned from the reports should be provided for the professionals that sent them **(!!!)**. This feedback encourages and consolidates the reporting process. Feedback acts on the datum generated and encourages additional reporting; in its absence, reporters are discouraged from reporting again.

The information service should also encourage (!!!) communities, hospitals, universities, and professional associations to originate, design, and develop active pharmacovigilance programs for special populations (children, the elderly, pregnant women, prevalent pathologies) and the drugs that require it.

4.3 Documentation

Good documentation is fundamental to a quality assurance system and good pharmacovigilance practices.

It is important because what is reported can produce signs; thus, the quality of the reporting is critical for proper assessment of the relationship between the drug and the adverse events.

4.3.1 Characteristics of Reporting

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

Active pharmacovigilance methodologies are as important as the spontaneous reporting, since they provide specific relevant data on special populations and drugs. For example: Prescription Event Monitoring (PEM), Case-Control Surveillance, and Record Linkage between different databases. Finally, data on the consumption or use of drugs are important for evaluating their safety. Without a doubt, it is essential to promote these types of programmed study to improve patient safety and implement them together with the spontaneous reporting system.

Adverse event reporting by the National Pharmacovigilance System is **voluntary, spontaneous, and confidential**. It is especially useful in detecting signs of rare, serious, or unanticipated adverse reactions.

In pharmacovigilance, an individual report of a case can be defined as *a report on a patient who has presented an adverse medical event (or an alteration in laboratory tests) that is suspected to be caused by a drug.*

Reporting is done on a reporting form or yellow card (Annex I, see model), as well as other printed materials for reporting international adverse effects for the purpose of prescribing treatment, care, or precautions. Any suspected therapeutic deficiencies associated with the drugs marketed in the Region are also reported there.

The content of the cards can vary from country to country, but all have four sections to complete: patient data, description of the event, drug data, and reporter data.

This is the basic information **(!!!)** that they should contain:

- 1) Patient data: weight, age, sex, ethnicity (in certain countries), and a brief clinical history (when relevant)
- 2) Description of the adverse event: nature, location, and intensity, including the date of onset of the signs and symptoms, their course, and outcome
- 3) Data on the suspect drug: generic or trade name, dosage, method of administration, date treatment began and ended, indications for use, expiration date, lot number, and manufacturer
- 4) Data from the patient on his disease: baseline medical condition before starting the medication, co-morbidities, relevant family history of disease
- 5) Concomitant drugs. All other drugs taken by the patient (including self-medication): names, dosage, methods of administration, start and end dates
- 6) Data on the reporting professional. Name and address of the reporter; this information should be considered confidential and used only to confirm or complete the data or follow-up on the case

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

- 7) Risk factors (for example, alteration of renal function, exposure prior to taking the suspect drug, known allergies, recreational drug use)
- 8) Documentation on the diagnosis of the event, including the methods used in the diagnosis
- 9) The clinical course of the patient and outcome (hospitalization or death). Patient outcome might not be available at the time the report is sent; in such cases there will be a follow-up.
- 10) Relevant laboratory findings during the baseline, therapy, and subsequent therapies, including blood levels
- 11) Information on the response after withdrawal and re-exposure
- 12) Any other relevant information (e.g., other details related to the event or information on benefits received by the patient, if relevant to the assessment of the event)

For reports on medication errors, a good report also includes a complete description of the following information **(!!)**, when available:

- 13) Products involved: including the trade name and manufacturer, dose, dosage form, and size of the container
- 14) Sequence of events leading up to the error
- 15) Work environment where the error occurred
- 16) Types of staff involved in the error, types of errors, and factors that can contribute to them

There is no single reporting form for spontaneous reporting systems. This was studied by WHO, which found that having one would not be the most effective strategy. This means that only guidelines indicating the

basic data needed for the design of the reporting forms have been prepared, as described in the preceding paragraphs. The principles should be applicable in any language¹³.

Many authorities believe it important to include a narrative section to convey meaning. The narrative section provides an opportunity to capture the rich context and thread of the history, making it possible to see the conditions in which the error or effect should be examined and understood. In fact, some people believe that only narrative reports are capable of providing significant information on the effects of the event⁹. Systems that allow open narratives require additional resources to analyze and interpret the data, unlike systems with a standard format, fixed fields, and predefined choices, in which the data are read, rapidly entered, and easily classified, permitting analysis in addition to a low cost.

Another consideration is the **impact of the reporting on the reporter**. Giving reporters the opportunity to tell their story implies that their observations are valuable. When a reporter can count on a measured and nonpunitive response, the state of alert on patient safety is raised and he feels a responsibility to report.

A national pharmacovigilance system can include a type of *compulsory reporting*, which will be applied to drugs subject to intensive monitoring. This category includes drugs useful in the treatment of certain diseases but, because of their characteristics, can produce serious undesirable effects. Not only for drugs, but special populations as well (the elderly, children, pregnant women, certain pathologies).

Concerning active pharmacovigilance studies, the forms and questionnaires are specially designed at the time the study objectives and number of patients in the study are established. In this case, other relevant data will be included, such as:

- Identification number of the patient in the study
- Neighborhood, district, city where he/she lives
- Contacts

The details to be entered will depend on the study, as in 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 areas (for example, four distributions per year). It may be effective to include forms with prepaid postage in the national formularies, drug bulletins, or professional journals. Other expeditious reporting methods are telephone, fax, and e-mail or Internet forms, when the technology is available.

¹³ The need for a generic form for spontaneous reporting of drug related problems *Sten Olsson, the Uppsala Monitoring Centre*.2007.02.01 . En línea. < <http://www.who-umc.org/graphics/13018.pdf>> [Accesed October 2008].

4.3.2 Other Documents

In addition to yellow cards, there are other documents that describe the operations of a pharmacovigilance center, such as manuals on quality and operating procedures or records.

In order to conform to good practices, the documentation should have the following characteristics¹⁴:

- Documents should be designed, prepared, modified, and distributed on the basis of their usefulness.
- Documents should be approved, signed, and dated by the appropriate authorized personnel.
- Documents should be written unambiguously; their title, nature, and purpose should be clear. Their distribution should be orderly and easily confirmed.
- The documents reproduced should be clear and legible. When reproducing working documents from the original, there should be no errors in the reproduction process.
- The documents should be periodically reviewed and updated. When a document is modified, a system should be in place to prevent unintentional use of the older documents.
- Documents should not be handwritten; however, when they require the introduction of data (entries), the entries may be inserted in a clear and legible hand in indelible ink. Enough space should be left for them.
- Any change in a written datum in a document should be signed and dated; the change should not prevent the initial datum from being read. If necessary, the reason for the change should be indicated.
- Documents related to a single report of a suspected adverse reaction should be kept in the same file or, in its absence, there should be a clear reference to their location, so that significant activities related to the report, documentation, and/or its assessment can be followed.
- 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 drugs. This book should contain other data such as an algorithm of imputability, communication with the reporter, and other comments. This book can be created with a computer database.
- The data can be entered through electronic data processing systems, photographic systems, or other reliable methods. However, detailed procedures for the system used should be maintained and the accuracy of the entries should be verified. If the documentation is processed electronically, it can be entered or modified on the computer only by authorized individuals, and a record should be kept of any changes or deletions. Access should be restricted through the use of passwords or other security measures, and the results of the introduction of basic data should be verified independently.
- The confidentiality of the patient and reporter data should be preserved through the use of codes. Electronically stored report files should be protected through back-up copies, so that the data can be easily accessed during the time they are stored

¹⁴ Guía para Autoridad Sanitaria Buenas prácticas de Farmacovigilancia y Evaluación Farmacoepidemiológica. Documento en discusión Segunda versión elaborada por los docentes Claudia Vacca, José Orozco, Esperanza Holguín, Julián López, María Fernanda Parra, Giovanni Montoya. En el marco del convenio 07 de 2007 INVIMA.

Entries: All activities in connection with the receipt, follow-up, assessment, 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 reporter should also be maintained.

4.3.2.1 Manuals

Manual on quality: This document describes the objectives, methods, and procedures for quality assurance. It is an important document that enables internal and external staff to learn about the existing quality assurance system.

Manual of procedures: This document should provide an orderly and logical description of the standard operating procedures used in the center and the relationships among them to give readers an idea of the entire 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 properly executed, it must be held against a preestablished standard.

The operational procedures for the work (also known as SOP, for *Standard Operating Procedures*) are a very important part of the documentation for a quality assurance system and are defined as detailed written instructions to achieve uniformity in the organization of a specific activity. They are essential for internal or external audits.

Written procedures and entry procedures must be available (!!!) to provide orientation for activities in the following areas:

1. 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
2. Administrative activities.
 - Entry of data in the database
 - Documentation file
 - Protection of computer files
 - Data modification

3. Assessment and preparation of reports

- Acceptance and rejection of reports
- Preparation of feedback information
- Assessment and coding of reports
- Preparation of reports
- Prevention of duplication
- Detection and management of warning signs

All standard operating procedures must require 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 has 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 standard operating procedures
- Circulation of copies: The people or departments or sections that should have a copy should be indicated.

4.3.2.3 Additional Documentation

The additional documentation is anything that will complete the information contained in the data collection form for adverse reactions. It can consist of reports 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, assessment report, coding report, reports by experts, etc..

This documentation should be filed in the same file as the original report as long as it is kept.

4.4 Computer Systems

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

- System operations
- Maintenance
- Security
- Control of access and back-up copies

This means making back-up copies of the information on a regular basis (!!!). The records should 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 make changes in the data. Access to the documentation should be limited to authorized personnel, and a record should be kept of any access to the data (!!!).

Any changes in the original data during processing should be made in a manner that permits access to the earlier data and comments, guaranteeing their traceability. The reason for the change should be indicated and kept on record (!!!).

Periodic data quality controls should be performed to detect systematic data coding and processing errors (!!).

The personnel in charge of the center will decide which computer software to use. Information and assistance can be obtained from the UMC. The database should have the fields necessary for evaluating the case analysis and follow-up. It may not be cost-effective to use improvised computer software for processing reports on adverse reactions. Commercial software is available that has been adequately tested and can be adapted to the user, based on local needs, including indigenous languages.

4.5 Management of the Reports

To manage all the information from a center, it is important to have human resources with technological tools (!!!) that allow for feedback that is ongoing, timely, and valuable to the authors of the report. This encourages reporting activities and their use in supporting processes of analysis and research.

Management of the reports means that when the National Pharmacovigilance Center receives the yellow cards, it carries out the following activities:

- Reviews all the reports conducted by health professionals. When the report comes from a health professional who is not a physician, it is recommended that there be some way to obtain complementary information from the prescriber or the physician responsible for the patient. When the notifier is a consumer or a patient, it is important to obtain permission to contact the medical professional who provided the service in order to obtain accurate medical 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 of the suspicious drugs and one or more of the adverse reactions. Furthermore, it is important to know the date of onset of the adverse reaction.
- Makes the maximum effort to obtain complete and necessary information according to the characteristics of the adverse event. This basic information allows for generating signals or alerts, but is insufficient for evaluation of the event. If the initial report is not in writing, it should be validated.
- Follows up on incomplete reports, mainly when they refer to serious or unexpected adverse events, in order to obtain additional information from the initial notifier and/or from other available source

documents, such as the hospital report, results of laboratory tests, the report of the specialist, prescriptions, or others.

- Establishes procedures to promote reporting among health professionals, with a particular emphasis on reports of unexpected or serious adverse reactions and on reports that involve drugs recently put on the market.

In the initial stages managed by the center, case reporting can be handled manually. When the number of reports increases, it is recommended that a computerized system be used to facilitate the compilation and handling of cases classified according to suspicious drugs and adverse reactions.

The computerized system used should include a hierarchical index of drugs that allows for classification of the drug by generic and brand names and by therapeutic category. Similarly, a hierarchical terminology of adverse reactions should be used. This is necessary to enter the specific record of detailed information on the case, and also allows for collecting the information at higher levels. (See section 4.5.3, "Data Coding and Recording," for the recommended coding.)

4.5.1 Methods for Sending Reports

Methods for sending the reports (e-mail, fax, Internet, mail, telephone) vary according to local infrastructure and technology:

- Mail, fax, and telephone calls are the most widely used, since they are the most available (!!!).
- A systematic process should be organized for reports received by e-mail or the Internet; this can be very fast and easy, but it can also be expensive to establish the technical infrastructure (!!).

4.5.2 How to Improve Reporting

Procedures should be established to promote reporting by health professionals (!!!), including through:

- Easy access to the yellow cards (or forms, tickets, files) with prepaid postage and other means of reporting such as e-mail or through the Web page
- Acknowledgement of receipt for each report of a suspicious adverse reaction and a personal letter or telephone call to thank the notifier
- Providing feedback to notifiers in the form of articles in journals, adverse reaction bulletins, or information sheets
- Participation of personnel from the centers in scientific meetings or educational courses, both at the undergraduate and postgraduate levels
- Collaboration with local pharmacovigilance committees; collaboration with professional associations
- Integration of pharmacovigilance into the development of clinical pharmacy and pharmacology in the country.

4.5.3 Data Coding and Recording

The coding and recording of the data for the center should be defined:

- The drug surveillance system should use categories of **coding and terminology (!!!)** adopted at international regulatory forums (such as international conferences on harmonization).
- The coding should be carried out in accordance with provisions in the coding manual.
- The national or coordinating center should carry out periodic quality control of data with a view to detecting systematic coding and loading errors (!!!).
- Management of the data should allow for protecting the identity of the people involved (!!!), both the notifier as well as the event, as defined in **Characteristics of the Reports**.
- The integrity, accuracy, reliability, consistency, and confidentiality of all information should be guaranteed (!!!).
- For each report, the date of receipt should be recorded and assigned an identification number (!!!).

Internationally-accepted terminology should be used for the drugs and the adverse reactions:

- The names of drugs should be recorded in a systematic manner, using, for example, the *WHO Drug Dictionary* that is based on the International Nonproprietary Name (INN) nomenclature and WHO's Anatomical Therapeutic Chemical (ATC) classification.
- For the coding of adverse reactions, either WHO's Adverse Reaction Terminology (WHO-ART) or other internationally-accepted terminology such as the *Medical Dictionary for Regulatory Activities* (MedDRA) should be used to facilitate cross-national comparisons of the results and for the international transmission of data.

Special attention should be given to making the information compatible with the report requirements established in the WHO's International Pharmacovigilance Program. As already mentioned, detailed instructions can be requested from the Uppsala Monitoring Centre (UMC, the field name of the WHO Collaborating Centre for International Pharmacovigilance) on how to organize the computerized data of each report for its transmittal to the WHO database. Recently, the MedDRA has been implemented in the Vigibase (the database of the UMC). This is a very important step in the detection of symptoms¹⁵ and it helps in information exchange, education, training, and research on adverse reactions as well as their evaluation.

4.5.4 Inspection of the Database

A database of reports on suspected adverse drug reactions is an important source of information for the detection of signals relating to safety, prompting the need to develop studies to confirm, characterize, quantify, and assess those signals.

¹⁵ "The UMC and the International Conference on Harmonization MedDRA Management Board Announce MedDRA's Implementation in Vigibase Uppsala," March 17, 2008. Online: <http://www.ich.org> (accessed in September 2008).

Toward this end it is necessary that both local databases and those of each institution be linked to databases that compile regional and global information for the purposes of pharmacovigilance described in section 4.5.3.

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

Necessary measures should be taken to ensure the security and confidentiality of the above-mentioned information on adverse events (!!!) regardless of the manner in which it is recorded (paper, electronic, etc.), as well as in the processing of pharmacovigilance data.

It will be evaluated as follows:

- In loading the database it is very important to verify that all the data fields are complete in accordance with the database instructions (!!!).
- The severity of the illness of the patient will be recorded as the principal adverse event (!!!).
- Define causality: The definitions of causality of WHO and Orange's algorithm or the Food and Drug Administration (FDA) algorithm (Annex III) will be used as the common methodology for evaluating the causal relationship between suspicions of an adverse drug reaction and pharmacological treatments.
- Review: The designated center will review the data from other peripheral centers, organizing the information that will be sent to the National Center twice monthly (on the 15th and 30th of each month). Only one transmittal will be made in December, on the 20th.
- The country-specific database can be used for periodic reports, research on adverse drug reactions, education, system feedback, consultations on information, and theses for BA degrees, in a specialty, or for Master's or doctorate degrees, with the principle of confidentiality always maintained (!!).

4.5.5 Report Evaluation

For the reports to impact safety issues, the analysis of experts and the dissemination of lessons learned are necessary. Simply collecting data contributes little to advances in patient safety. The analysis of experts and the supervision of data are necessary to determine monitoring trends. **The response system is more important than the reporting system.**⁹

The following aspects can be distinguished in the evaluation of case reporting:

a. Quality of the information: Completeness and integrity of the data, quality of the diagnosis (monitoring). The basic elements of an individual report were outlined in **Characteristics and Management of the Report**.

b. Coding: As already noted in the previous point, the names of the drugs should be recorded in a systematic manner (*WHO Drug Dictionary*) or through WHO's ATC classification (an anatomical-

therapeutic-chemical classification of the drugs). For the coding of adverse reactions, the WHO-ART or MedDRA described in **Coding and Recording of Data** should be used.

c. Importance: Regarding the detection of new reactions, the regulation of drugs, or the educational or scientific value, the following questions, in particular, can be asked:

New drug? Commercial drugs that have been on the market for less than five years normally are considered “new drugs.”

Unknown reaction? For example, a reaction not included in the authorized Technical File or Summary of Product Characteristics (SPO). It is also important to know whether the reaction is described in the literature (for example, in the National Formulary, in Martindale, or in *Meyler’s Side Effects of Drugs*) and to consult the UMC as to whether there are antecedents in other countries.

Serious reaction? This is the magnitude of the effect induced by an adverse reaction in an individual, classifying it as mild, moderate, or severe, according to the effect or lack of one, and to the extent that it affects the daily activities of the patient.

d. Identification of duplicated reports: Certain characteristics of a case (sex, age or date of birth, dates of exposure to the drug, and others) can be used to determine if a report is duplicated.

e. Evaluation of the causality or imputation: Different approximations have been developed to make a structured determination of the probability of a causal relationship between exposure to the drug and adverse effects, such as that of the WHO Programme for International Pharmacovigilance (see Glossary). These systems are based mainly on the following aspects: *the temporary relationship* between administration of the drug and the event, the *medical or pharmacological plausibility* (signs and symptoms, laboratory tests, pathological findings, mechanisms), and the *probability or exclusion* of other causes.

For the complete evaluation of the reports the following questions can be asked:

Is there an alternative explanation for the reaction observed?

Were other drugs administered that were not cited in the report?

Is it certain that the patient took the drug according to the indications?

Had the patient previously taken this drug or another similar one?

How many cases of this new reaction have been reported to the Regional or National Center or to the UMC?

Not all the cards contain this information; efforts can be made to obtain additional information from the notifier by telephone or e-mail. In general, the data commonly requested describe possible underlying illnesses, other drugs taken by the patient that might not have been mentioned in the original report, effects of the same or similar drugs when they were taken previously, or other relevant information (such as the dosage, the manner in which the drug was administered, duration of the treatment, age). Additional infor-

mation is almost always requested when the reports describe severe pathologies, previously unknown adverse reactions, or drugs recently introduced as part of treatment.

4.5.5.1 Severity of the Reactions

The severity of the reactions is classified in four categories:

- a) **Lethal or fatal:** The reaction contributes directly or indirectly to the death of the patient.
 - b) **Serious:** The reaction directly threatens the life of the patient, and can require the patient's hospitalization. (e.g., pulmonary embolism, anaphylactic shock)
 - c) **Moderate:** The reaction interferes with the patient's habitual activities, and can require the patient's hospitalization or absence from school or work without directly threatening the patient's life (acute dystonia, hepatitis colestasica)
 - d) **Slight:** Signs and symptoms are easily tolerated, do not require treatment, are usually short-term, and neither interfere substantially with the patient's normal life nor prolong hospitalization (nausea, diarrhea).
- The assessment of severity requires an individualized study of each report on the duration and intensity of the reaction.

4.5.5.2 Chronological Sequence

The elapsed time between the start of treatment and the appearance of the first manifestations of the adverse reaction can be measured as follows:

1. Previous administration of the drug and appearance of the episode described, always and when the temporary sequence is compatible with the action mechanism of the drug and the physiopathological process of the adverse reaction.
2. Administration of the drug prior to the appearance of the episode described but not totally consistent with the pharmacology of the preparation and/or physiopathological process; for example, agranulocytosis that appears three months after withdrawal of the drug.
3. Sufficient information is not available to determine the chronological or temporary sequence.
4. According to the data of the report, there is not a reasonable temporary sequence between the administration of the drug and the appearance of the adverse reaction, or that sequence is incompatible with the action mechanism and/or the physiopathological process. For example, a neoplasm that appears a few days after initiation of the treatment.

4.5.5.3 Causality or Imputability Relationship

For evaluation of the cause-effect relationship (causality and imputability), the Orange algorithm and collaborators are applied (Annex III). It consists of a scale of probability that includes the temporary sequence between the suspicious drugs and the appearance of the clinical symptoms, the plausibility of the causal relationship (taking into account the previous description of the reaction in the medical literature or the known pharmacological properties of the drug), the outcome of the reaction after withdrawal of the drug, the eventual repetition of the clinical episode described with the readministration of, or reexposure to, the suspicious drug, and the possible existence of alternative causes. It also includes the existence of addi-

tional information based on complementary research directed toward ruling out other nonpharmacological etiologies. It has the advantage of being internationally accepted and user-friendly. (See Annex III for Orange's algorithm as well as the algorithm used by the FDA.)

In accordance with Orange's algorithm, suspected adverse reactions remain classified in the following four discreetly proposed categories: 1) Adverse reaction proven or defined, 2) Probable, 3) Possible, and 4) Unrelated or doubtful.

It is reasonable to postulate that in some instance the case presented does not represent an undesirable effect of the drug implicated, although there is a temporary relationship and no alternative cause. In this case a "conditional" category of causality would be added.

1. **Proven or definitive (*certain*):** A clinical event, including alterations in the laboratory tests, that occurs in a plausible temporary sequence with regard to administration of the drug, and that cannot be explained either by the concurrent disease or by other drugs or substances. The response to suppression of the drug (withdrawal; *dechallenge*) should be clinically plausible. The event should be definitive from a pharmacological or phenomenological standpoint, using a conclusive reexposure procedure (*rechallenge*) if necessary,.

2. **Probable:** A clinical event, including alterations in the laboratory tests, that occurs in a reasonable temporary sequence with regard to administration of the drug. It is improbable that it is attributed to the concurrent disease or to other drugs or substances. Withdrawal (*dechallenge*) of the drug results in a clinically reasonable response. It is not necessary to have information on reexposure (*rechallenge*) in order to assign this definition.

3. **Possible:** A clinical event, including alterations in the laboratory tests, that occurs in a reasonable temporary sequence with regard to administration of the drug, but that can also be explained by the concurrent disease, or by other drugs or substances. The information with regard to the withdrawal of the drug can be lacking or unclear.

4. **Doubtful or unrelated (*unlikely*):** A clinical event, including alterations in the laboratory tests, that occurs in an improbable temporary sequence with regard to administration of the drug, and that can be more plausibly explained by the concurrent disease or by other drugs or substances.

WHO has added a fifth category:

5. **Conditional:** The temporary sequence is reasonable and the reaction would not be explained by the clinical status of the patient, but the case presented does not represent an undesirable effect of the implied drug.

Effect of withdrawal of the suspicious drug

1. The undesirable effect improves with withdrawal of the drug regardless of the treatment instituted, and/or there was a single administration. The recovery period is compatible with the pharmacology of the drug and with the physiopathological process.
2. The reaction does not improve with withdrawal of the drug, with fatal reactions excepted from this group.

3. The suspicious drug has not been recalled and the present case does not improve.
4. The medication has not been recalled and the case improves (the appearance of tolerance is excepted from this group).
5. There is no information in the report with regard to withdrawal of the drug.
6. The outcome of the reaction is fatal or the undesirable effect is irreversible. Here it is important to include congenital malformations related to administration of the drug during pregnancy.
7. Despite the drug not being recalled, the case improves due to the development of tolerance.

Effect of readministration of the suspicious drug

Readministration of the drug accidentally or induced in controlled conditions is a test of great diagnostic value, although it often may not be ethical. The reexposure can be:

1. Positive: The reaction appears again upon readministration of the suspicious drug.
2. Negative: When the adverse drug reaction does not recur.
3. There was no reexposure, or the report does not contain information on readministration of the drug.
4. The undesirable effect is irreversible (death, congenital malformations, or reactions that leave permanent sequelae).

Existence of an alternative cause

Alternative causes are also evaluated. They can be as follows:

1. The alternative explanation is more important than the causal relationship to the drug.
2. There is a possible alternative explanation, but it is less important than the adverse reaction to the drug.
3. There is not sufficient information on the card to be able to evaluate the alternative explanation.
4. All the data are not available in order to rule out an alternative explanation.

This evaluation allows for summarizing all the information necessary to assess the causal relationship between the drug and the adverse reaction.

4.5.5.4 Mechanisms of Adverse Reactions

To devise the mechanism by which adverse reactions to drugs occur, this section presents some drawbacks derived from the lack of knowledge of all the properties of the administered drug as well as the mechanism that produces the adverse reactions. The classification proposed by Rawlins and Thompson is the most accepted. According to this classification, adverse reactions produced by drugs could be subdivided into two major groups in accordance with the production mechanism: those that are normal but increased pharmacological effects (Type A or *augmented*), and those that are abnormal and unexpected pharmacological effects if the pharmacology of the drug is taken into account (Type B or *bizarre*).

Type A effects (*actions of the drug*): These are due to pharmacological effects (increased). Type A effects tend to be quite frequent, dosage-dependent (for example, more frequent or intense with higher dosages), and can often be avoided by using a more appropriate dosage for the individual patient. These effects can normally be reproduced and studied experimentally and often are already identified before marketing. Interactions between drugs, especially the pharmacokinetic interactions, can be classified as Type A effects, although they are restricted to a subpopulation of patients (for example, users of the drug that interacts).

Type B effects (*reactions of the patient*): These characteristically happen in only a minority of patients and show a minimal or no relationship to the dosage.

These effects normally are infrequent and unpredictable, and they can be serious and difficult to reproduce in experimentation. Type B effects can be both immunological and nonimmunological, and occur only in some patients with often-unknown predisposing factors. Immunological-type reactions can range from eruptions (*rashes*), anaphylaxis, vasculitis, and inflammatory organic injury up to very specific auto-immune syndromes. There are also Type B nonimmunological effects in a minority of predisposed patients, such as those who are intolerant due to a birth defect of the metabolism or to deficiency acquired with regard to a given enzyme, with the result being an altered metabolism or an accumulation of a toxic metabolite. As examples, there are cases of aplastic anemia by chloramphenicol and hepatitides by isoniazid. Type B adverse reaction to drugs can be due to unknown or idiosyncratic causes and immuno-allergies:

Idiosyncratic: The pharmacological effect is qualitatively different. These phenomena have a genetic base in their origin.

Immuno-allergies or hypersensitivity: These are always secondary to the antibody formation by the immune system. They are the most frequent dose-independent reactions.

Adverse reactions to drugs determined by allergic factors are mediated by the immune system, and result from a prior sensitization to a particular drug or to another substance of similar structure. For a substance of low molecular weight to be able to originate an allergic reaction, it is necessary that it or some of its metabolites act as haptens, joining in an endogenous protein to form an antigenic complex. These complexes induce the antibody formation after a latent period. A subsequent exposure of the organism to the substance produces an antigen-antibody interaction that triggers the typical reactions of allergy. Small amounts of an allergen can cause serious reactions. The results of the reaction are amplified by the release of histamine, leukotrienes, prostaglandins, and other related substances.

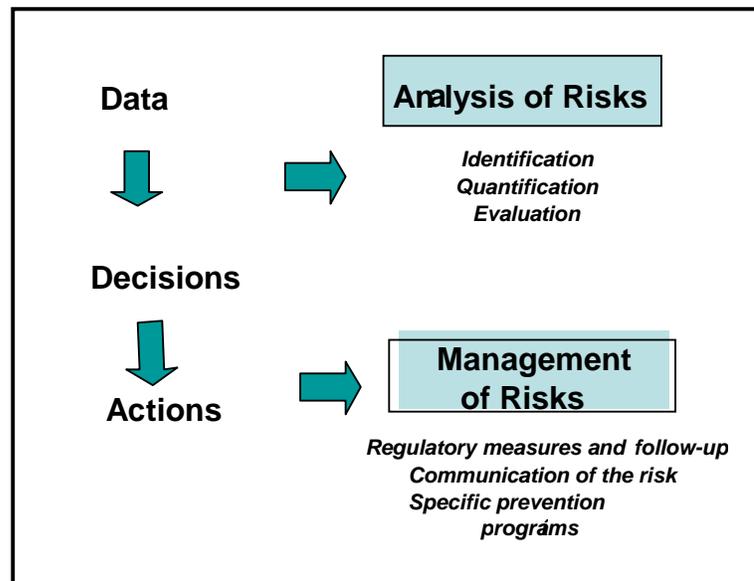
It has been proposed that **Type C effects** would be those associated with prolonged treatments (for example, papillous necrosis and renal insufficiency due to the prolonged use of analgesics). **Type D** (*delayed*) effects would be those that are delayed, alien to the treatment, and that appear some time after administration of the drug in the patients and even their children. These effects are infrequent; the most important are teratogenesis and carcinogenesis.

5. GOOD RISK ANALYSIS AND RISK MANAGEMENT PRACTICES

Pharmacovigilance mainly involves the identification of warning or safety signals. The risks of drugs once they are in the marketplace should also be analyzed and managed. In accordance with this, two phases can be defined: risk analysis and risk management.

Risk analysis deals with the identification, quantification, and evaluation of risks. Risk management deals with the implementation and monitoring of the regulatory measures adopted to communicate risks to health professionals and/or the population in general, and to determine preventive measures. Risk analysis is led by the data, while risk management is led by action. The decisions taken constitute a bridge between the two areas (Figure 1).¹⁶

Figure 1. Risk Analysis and Risk Management Diagram¹⁷



After the input of the data in accordance with good practices, risk analysis is carried out in three steps and risk management is then applied:

Risk identification
Risk quantification

¹⁶ WHO Drug Information, Vol. 18, No. 3, 2004, Safety and Efficacy Issues.

Risk assessment
Risk management
Risk communication

5.1 Identification of Risks

Generation of signals and evaluation of the causality of reports on individual cases and series' of cases.

A signal is the information communicated about a possible causal relationship between an adverse event and a drug when that relationship is unknown or not well documented. A safety signal or alert refers to a concern regarding an excess of adverse events compared with those that could be expected to be related to the use of product.¹¹ The signals usually indicate the need for future research, which may or may not lead to the conclusion that the drug caused the event. After a signal is identified, it should also be evaluated if it poses a potential risk to safety, and to determine whether other actions should be taken.

The signals generated through the voluntary report or other methods are evaluated, and a careful review of cases as well as a search for additional cases will be carried out. These signals can come from post-marketing studies or other sources, such as preclinical data and events associated with other products of the same pharmacological classification, and are mainly detected by:

- Descriptions of isolated patients
- Publication of the cases in the biomedical literature
- Spontaneous reports to the pharmacovigilance system
- Observational studies in populations: case and control or cohort studies, and
- Experimental studies: clinical trials.

It is possible that a single well-documented reported case can be seen as signal, particularly if it describes a positive reexposure or if the event is extremely rare in the absence of the drug being used.

5.1.1 Descriptive Analysis of a Series of Cases

An evaluation will be conducted on the causality of individual cases, and as to whether one or more cases can indicate a safety concern that merits an additional investigation.

The following will be taken into account (!!!) in the evaluation of the causal relationship between the use of a drug and the occurrence of the adverse event:

- The occurrence of the adverse event during the time period expected; for example, an allergic reaction that occurs within days of therapy, or cancers that develop after years of therapy.
- The absence of symptoms that relate the event to the exposure.
- The evidence of positive discontinuation of the treatment or positive reexposure.

¹⁷ Presentation by Francisco J de Abajo, Pharmoepidemiological Pharmacovigilance Division, Spanish Agency on Drugs and Health Products, at the 11th Conference of International Regulatory Authorities (ICDRA). 16-19, Madrid, Spain.

- The consistency of the event with the pharmacological/toxicological effects established in the drug, or for the vaccines, the consistency with the established immunological mechanisms of the injury.
- The consistency of the event with the known effects of other drugs of the same classification.
- The existence of other evidence of support (preclinical studies, clinical trials, and/or pharmacoepidemiological studies).
- Absence of alternative explanations to the event (for example, no concomitant medications that could contribute to it); or no medical or premorbidity conditions.

As part of the review of cases, it is suggested that each case be evaluated based on the clinical content that is complete, but that there also be follow-up with the notifiers. It is important to eliminate duplications. In the evaluation, it is important to look at characteristics that could suggest a causal relationship between the use of the drug and the adverse events, including.

Also to be taken into account will be the categories recommended and used by WHO for the assessment of causality:

- Definitive
- Probable
- Possible
- Doubtful or unrelated
- Conditional

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

- Clinical manifestations, laboratory results, and the timeline of the event
- Demographic features of the patients with the events (for example, age, sex, race)
- Duration of the exposure
- Time of initiation of the exposure of the product to the adverse event
- Doses used in the cases, including labeled doses, the largest doses used, and the toxic dose
- Use of concomitant medications
- Presence of conditions of morbidity, particularly when the cause of the adverse event is not known; also if liver levels are low and there is renal deterioration
- Manner of administration (for example, oral versus parenteral) and the lots used in patients with the events
- Changes in the proportion of the report of the event during a time period or life cycle of the product.

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

Data mining consists of the nontrivial extraction of information that resides implicitly in data. This title encompasses a whole set of techniques directed toward the extraction of actionable knowledge implicit in

the databases. Such information was previously unknown and can be useful for some processes. In other words, the data mining prepares, questions, and explores data in order to take out their hidden information. For an expert, or for those responsible for a system, these data are normally not the most relevant, but rather the information that is encompassed in the data's relationships, fluctuations, and sections.

In the various steps of identifying and evaluating risks, systematic examination of reports of adverse events using data mining can provide additional information concerning reported adverse events that relate to drugs.¹¹ By applying *data mining* techniques on the basis of extensive data such as those available through the UMC or FEDRA,¹⁸ as well as the FDA, AERS¹⁹ or VAERS,²⁰ it is possible to identify an unusual adverse or unexpected event related to drugs that will guarantee future research.

Data mining can be used to increase strategies to detect existing signals, and it is especially useful for evaluating patterns, trends over time, and events associated with pharmacological interactions (!!). The use of data mining can provide additional information on the existence or characteristics of a signals such as the Gamma Poison algorithm,^{21,22} the Bayes theorem. Data mining is not a useful tool to establish causality functions between the product and adverse events.

Data mining is useful for identifying rare or unexpected events, providing timely information for the research that is carried out. Research can be conducted on the following (!!):

- New adverse events not indicated in the labeling, especially if they are serious
- An apparent increase in the severity of an event indicated in the labeling
- An increase in the frequency of rare but serious adverse events
- New interactions between drugs, drugs and foods, or drugs and supplements
- Previously unrecognized at-risk populations (for example, populations with specific racial or genetic predispositions or co-morbidities)
- Real or potential confusion regarding the name of a drug or its labeling, packaging, or use
- Concerns over the way a drug is used (for example, adverse events, defects in quality or therapeutic effectiveness, labeling with high dosages, or use by populations not recommended for treatment)
- Concerns over inadequate plans for potential implementation of action plans to minimize risk
- Other identified concerns regarding the monitoring systems established.

¹⁸ FEDRA (Database of Adverse Reactions of the Pharmacovigilance System of Spain).

¹⁹ Database of the Adverse Event Report System (AERS) of the FDA. Online: www.fda.gov/cder/aers (accessed in September 2008).

²⁰ System for the Reporting of Adverse Reactions to Vaccinations (VAERS). Online: www.vaers.hhs.gov (accessed in September 2008).

²¹ DuMouchel, W., and Pregibon, D., "Empirical Bayes Screening for Multi-Item Associations," *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining*. 2001.

²² Szarfman, A., Machado, S.G., and O'Neill, R.T., "Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the U.S. FDA's Spontaneous Reports Database." *Drug Safety*. 2002. 25(6): 381-92.

The results obtained with these methods will be analyzed by a multidisciplinary group of experts (!!!). The methods of mining current data generate scores of comparisons, the fraction of all the reports for a particular event, such as liver insufficiency, for a specific drug, the fraction of observed reports, with the fraction of reports for the same particular event for all the drugs.²³

The score generated by data mining quantifies the disproportion among the observed and expected values for a given drug-event combination. A potential excess of adverse events is defined as any combination of drug-event with a score that exceeds the specific threshold.

This should also be analyzed in the epidemiological context, which includes:

- A description of the database used
- A description of the data mining tool used (algorithm, events of the drugs, and stratifications of the analysis), an appropriate reference, and
- A careful individual evaluation of case reporting and other safety information relevant to a combination drug-event of interest, such as preclinical results, pharmacoepidemiology, and other available studies.

Estimation of frequency when there are incomplete observations

The problem of incomplete observations—patients who leave, monitoring losses, etc.—often comes up in estimating the frequency of adverse reactions. Although there are statistical methods to address this type of observation, we find that they are not commonly used in estimating the frequency of adverse reactions, and that missing data are simply ignored, which probably results in a more optimistic estimate of frequency.²⁴

Another problem in estimating the frequency of adverse reactions is that, except for when they concern serious or even fatal reactions, these reactions often occur 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 that these occur.

These problems and the estimation of the probability of an adverse reaction that has not yet occurred can be delved into further in the reference article.²⁵

²³ Evans, S.J., "Pharmacovigilance: A Science or Fielding Emergencies?" *Statistics in Medicine*. 2000. 19(23): 3199-209; Evans, S.J.W., Waller, P.C., and Davis, S., "Use of Proportional Reporting Ratios (PRRs) for Signal Generation from Spontaneous Adverse Drug Reaction Reports." *Pharmacoepidemiology and Drug Safety*. 2001. 10: 483-86.

²⁴ "Analysis of Data on Adverse Reactions." Prepared by Luis M. Molinero (*Alce Ingeniería*), Asociación de la sociedad Española de Hipertensión, Liga Española para la lucha contra la Hipertensión Arterial. May 2004. Online: www.seh-ielha.org/stat1.htm (accessed in September 2008).

²⁵ "Guidance for Industry Development and Use of Risk Minimization Action Plans." U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). March 2005. FDA.

5.2 Generation of Signals

It is the responsibility of technical pharmacovigilance personnel to periodically evaluate the information contained in the database for the purpose of identifying signals:

- 1 The signals generated should be discussed in meetings of the national or coordinating center, at which the relevance of their being discussed with the national regulatory authority should also be considered (!!!).
- 2 When it is determined that the signal generated constitutes an imminent public health problem, all of the pharmacovigilance centers should be notified immediately (!!!).

Two exemplary cases of how the generation of a signal or alert due to spontaneous reports led to the withdrawal of the drugs *ebrotidine* and *cerivastatin* can be analyzed.^{4,26}

5.3 Quantification of Risks

Quantification of the strength of association

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

The use of data on the consumption of drugs will permit an approximation of the denominator, expressing it in months or years of treatment based on the daily average dosage, or in prescriptions, in order to be able to calculate the risk.

5.3.1 Studies to Quantify Risks

In most cases this second step of risk analysis can only predict rigorously through analytic epidemiological studies. Different designs of the post-marketing monitoring studies that allow for quantifying risks can be used. These serve the purpose of verifying a hypothesis, that is, establishing causality between the presence of an adverse reaction to a drug and the use of a drug. The studies can include the following:

Observational analytic studies

These studies are classified into two major categories that address the selection criteria of the patients: cohort studies and case and control studies. The principal characteristics of each of them are described in general terms below.

Cohort studies

²⁶ Rodríguez J.M., Aguirre C., García M., and Palop, R. Farmacovigilancia. Farmacia Hospitalaria Capítulo 2.10. Online: http://www.sefh.interguias.com/libros/tomo1/Tomo1_Cap2.10.pdf (accessed in September 2008).

These studies, which are observational and analytical in nature, allow for determining incidence rates of adverse reactions induced by the drug.

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 time period. Static populations are used. Its measure of frequency is the cumulative incidence (number of new cases divided by the departing population that generates the cases). In contrast, open cohort studies use dynamic populations (those that exist naturally), the 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 periods of observation of each subject).

Cohort studies allow for directly estimating measures of both association (relative risk) and frequency (absolute risk). It is also possible to estimate the attributable risk (difference of exposed and unexposed incidences), a measure that is of great interest from a public health standpoint.

Event monitoring cohorts

Event monitoring cohorts have as their model the prescription monitoring studies that have been applied in New Zealand and England, with something similar in China dealing with contraceptives. The program developed by WHO to monitor antiretrovirals in developing countries has recently been implemented with this method in China.⁹ These are intensive pharmacovigilance studies conducted to obtain information on suspected adverse drug reactions in a manner that is systematic, of good quality, and complete, characterized by high sensitivity and reliability, particularly when it becomes necessary to determine the frequency of the adverse reactions and identify predisposing factors and patterns of use of drugs, among others things.

Event monitoring cohorts are studies of observational prospective cohorts of the use of drugs in patients who are the target population for that drug. In this case, all the adverse events are recorded, 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:

- Establish a cohort of patients for each drug and/or combination of drugs;
- Record the adverse events of the patients in the cohorts over a defined period of use of the drug.

The cohorts should be complete and as representative as possible. Recording all of the adverse events is essential in order to avoid losing any new signals. In these cases, appropriate monitoring procedures should be designed and established to obtain information on any adverse event and to train the personnel in the methodology.

These studies have many advantages, since they produce indices as well as a complete description of the profile of the adverse reaction to the drug of interest and its characterization in terms of age, sex, duration, and risk factors. Registries can be established of pregnancies and all deaths, and rapid results for the defined population can be produced.⁹ These advantages help to overcome the deficiencies of the spontaneous notification system, although that system remains essential because it covers the total population and its time is not limited. The two systems are complementary.

Case and control studies

Patients with an adverse reaction are identified and compared with the control patients, who have the same characteristics but do not suffer from the adverse reaction.

In this type of study, patients are selected according to how they present or do not present a given disease. The cases will be patients with the disease and the control patients will be selected randomly from the same source population from which the cases arise, although they do not have the illness at the time of their selection.

This design is especially useful when one wants to study adverse reactions that are infrequent or that require long exposure periods or induction in order to be produced, since the inclusion of a sufficient number of cases is guaranteed without the need for following all the subjects of the source population from which the cases are derived, as would occur if a cohort-type design were selected. Another advantage of the case and control studies is that they allow for analyzing the association of the disease with various factors at the same time.

Frequently used in case and control studies is a measure of association known as the odds ratio. If the control patients are a random sample from the source population, it is easily shown that the odds ratio and relative risk coincide.

It is important to emphasize that although passive monitoring, spontaneous reporting, is really valuable, it is necessary to carry out active monitoring, since it provides greater sensitivity to identify, confirm, characterize, and quantify possible risks. Active pharmacovigilance activities include the design and development of studies of post-marketing use and/or safety that permit a more formal approximation of risk prevention.

Controlled clinical trial

This is the paradigm of clinical research and the basic tool to evaluate the efficacy of the drugs. Its application in the evaluation of post-marketing safety, however, is generally not considered to be efficient, except in those cases in which the safety problem constitutes a very defined objective, is sufficiently frequent, and, especially, when there are concurrent confusing difficult adjustment factors (especially confusion regarding indications).

5.4 Risk Assessment

5.4.1 Assessment of the Benefit/risk ratio

The third step of the analysis is to judge whether the risk identified and quantified is acceptable for the society and under what conditions. In addition to the data on the risk of the drug, its potential benefit should be considered as well as the risks and benefits of the therapeutic alternatives, when they exist. Ultimately, the aim is to try to establish if the benefit/risk ratio of the drug continues to be favorable.

It is difficult to quantify this relationship because, among other reasons, the benefit and risk do not tend to find expression in the same units, as for example in the case of deaths prevented by the treatment versus deaths induced by adverse reactions. But even in this particular situation, it is highly probable that the number of deaths does not entirely take into account either the benefit of the drug, such as the quality of life, or all of its risks. Another difficulty is that there is not a clear definition of the limit that would separate what is acceptable from what is unacceptable beyond the circumstance of each individual.

Assessing the benefit/risk ratio is a process that requires data, to which it is then necessary to add an element of value. To assess the social acceptability of the associated risks, it is necessary to employ the technical assistance of experts or expert committees related to risk quantification and assessment.¹⁴

- Supervision, approval, and advisory services in pharmacoepidemiological studies
- Systematic review of the scientific literature and of any other information on adverse drug reactions, and on the motivating principals behind the reports

5.5 Risk Management

Risk management is an iterative process of assessment of the benefit/risk balance of a drug. It consists of developing and implementing tools to minimize risk while preserving benefits. These tools imply the continuous reevaluation of the benefit/risk balance, which leads to making adjustments, if appropriate, to minimize risks, with a subsequent increase in the benefit/risk balance. This process should be ongoing over the life cycle of the product. With the results of the risk assessment, those responsible for a product will make decisions to diminish risk.^{14, 25}

The innovative concept of risk management systems in entities that regulate drugs was introduced into the European Union, the United States, and Japan, taking into consideration the ICH efficacy and quality guides for the management of risks in terms of quality and pharmacovigilance risk plans. They constitute a stage of superior development in quality assurance, safety, and efficacy of the products and processes that should be assessed for their inclusion in our context.

Once of the risk analysis phase is concluded, everything is ready to undertake the timely actions that we call risk management. From the specific standpoint of pharmacovigilance, there are three relevant actions:

- Adopt administrative measures to reduce risk

- Communicate to health professionals and patients the existence of the risk, the measures adopted, and the recommendations in this regard
- Establish specific prevention strategies.

Activities related to risk management include (!!):

- Preparation, approval, and sending of the information interinstitutionally or beyond.
- Management of the response to requests for information from the notifiers and the general public
- Communication of urgent restrictions on drugs for safety reasons and modifications of the conditions for authorization related to pharmacovigilance
- Immediate evaluation and communication of changes in the benefit/risk ratio of the drugs to the pharmaceutical industry and to health professionals
- Coordination of capacity building, training, and advisory services for members of the reporting network and health professionals
- Dissemination of information and education to the general population on problems related to drugs and on the appropriate use of drugs.

5.5.1 Risk Minimization Plan

To ensure the effectiveness and safety of drugs, pharmaceutical laboratories should try to maximize the benefits and minimize the risks (!!!). For most drugs, measures to minimize risks are sufficient. These measures involve a good description in the prospectus on the uses of the drug and on its safety and efficacy, as well as constant updates provided by post–marketing evaluations with regard to new benefits, formulations, and indications. However, it is important and advisable to design a Plan for the Minimization of Risks.²⁵

Such a plan represents a strategic safety program to meet specific targets and objectives to minimize the known risks of the drugs while preserving their benefits. It can also be regarded as a selective safety action plan, such as that defined by the International Conference on Harmonization (ICH *E2E: Pharmacovigilance Planning*). The development of a risk minimization plan is applied in the preclinical, clinical, and post-marketing phases of the drugs. An effective plan can only be developed with the appropriate information from these studies on efforts to use the drug and on the population.

To meet the plan’s targets, which will depend on the frequency and severity of the specific risk, it is recommended that the plan be developed with practical, specific, and measurable objectives. Currently, a variety of tools are used in risk minimization plans. They can be classified in three categories:

- Education oriented and directed toward communicating the risks and the patterns of safety to health professionals. These involve specific charts and training;

- Systems to record processes, or a manner in which to adopt uses and prescriptions, that reduce risk. These include training with evaluation, patient consent, and data collection systems in pharmacies, among other things; and
- Systems of access that guide the use, prescription, and dispensing of drugs to the appropriate populations, and that confer greater benefits and minimize specific risks. These include prescription by specialists, marketing limited to certain pharmacies, and dispensing to patients with laboratory tests.

In the design of the plan, analysis should always be carried out on a case-by-case basis in accordance with the drug, taking into account the following (!!!):

- 1) The known benefit/risk situation and relationship. It is necessary to evaluate:
 - The type, magnitude, and frequency of risks and benefits
 - Greater-risk populations as well as those that stand to most benefit
 - The existence of alternative treatments
 - The reversibility of the observed adverse events
- 2) The prevention of adverse events
- 3) The probability of benefits.

It is also important that the design of the plan be evaluated during its development, and that its tools be evaluated as well, to ensure that it is really cost effective.

5.5.2 Administrative Measures for Risk Reduction

The national regulatory authority and the pharmaceutical laboratories, as those responsible for the authorization and marketing of the drug, are in charge of taking the necessary steps to reduce the risk that can be posed by its use. The decision to put in place regulatory measures should take into account the social acceptability of the risk in relation to the benefit, although other factors tend to play a part when the information available is insufficient or uncertain. The measures can range from reporting on the new risk to immediate withdrawal of the drug. This decision should be based on evidence, experience, objectivity, and transparency.

The administrative measures to reduce risk known as *Health Safety Measures* will depend on the risk detected and can be classified in accordance with the risk:

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

1) *Imminent or serious risk to health:*

- Retaining lots of the drug or all of the product on the market
- Putting in place a quarantine

- Partial or total temporary closure of activities or services
- Closure of the pharmaceutical establishment temporarily, partially, or totally.

2) *Acceptable risk when used under any conditions*

Maintaining the status quo of the health registry or the marketing regime will be considered, and the following measures will be adopted:

- Inclusion of information on the information sheet and prospectus
- Introduction of information to clarify the specificities of the adverse reactions, giving recommendations for their treatment
- Introduction of new information to clarify the appropriate way to use and administer the product, the use of a low dosage, alternative therapies, or concomitant use of the drug with another drug in order to prevent risks
- The necessary information will be communicated on introduction of the drug, or in light of evidence that may have resulted in unfounded suspicions, or the absence of public health risks, as well as the adoption of additional measures to prevent the risks
- Release of lot(s) or all of the product held or in quarantine into the market.

3) *Acceptable risk when used only under certain conditions*

“Modification to the Health Registry or alteration of the marketing regimen” will be considered:

Modifications:

- Reduction of the recommended dose
- Restriction of therapeutic indications
- Elimination of one or more indications
- Introduction of new adverse reactions, counter indications, warnings, precautions, or drug interactions
- Elimination of information
- Restriction to certain population groups
- Recommendation to carry out clinical or analytical follow-up tests
- Restriction of the level of dispensing
- Exclusive use by hospitals
- Sale by medical prescription
- Use by selected services
- Special control drugs
- Programs for intensive monitoring or for use in mercy cases
- Restriction of the level of prescription to certain specialties
- Restriction of certain presentations
- Changes in the dosage form
- Changes in the container

- Modification of the presentation
- Changes in the formulation
- Changes in the composition
- Changes in storage or the form of preparation.

4) *Unacceptable risk when used under any conditions*

In the event that use:

- Turns out to be harmful or unsafe under normal usage conditions
- Turns out not to be therapeutically effective
- For any other reason poses a foreseeable risk to the health or safety of people
- Shows an unfavorable benefit/risk ratio.

Health Safety Measures:

- Withdrawal of lot(s) of the product from the market
- Withdrawal of the product or its active pharmaceutical ingredient from the market. Withdrawal can be immediate or progressive, at the request of the recording agency or by legal mandate. This measure carries with it in all cases the suspension or cancellation of the health registry or temporary health registry
- Seizure
- Destruction of the product
- Fines
- Transfer of the product to other uses in appropriate cases
- Temporary or permanent closure, partially or totally, of the activities or services
- Temporary or permanent closure of the pharmaceutical establishment partially or totally.

5.6 Risk Communication

5.6.1 Periodic Safety Updates

Periodic safety update reports are official documents that present all pharmacovigilance data on a particular drug in a given period, in accordance with its approval date.

The objective is that pharmaceutical laboratories participate in collection of notification data, evaluate the safety information collected and present it in a standardized way to the regulatory authority that approved the drug. They present the national and international experience on the safety of a drug, with these objectives:

- 1) Communicate all relevant new safety information from reliable sources.

- 2) Present a summary of the marketing approval status in different countries and any important modification on safety.
- 3) Periodically facilitate the opportunity to reevaluate safety and decide if the therapeutic information on the brand name drug needs to be modified.

Individuals have the right to be accurately and thoroughly informed about risks to their health from new technologies, and only in exceptional cases, to avoid a greater risk, could total or partial non-communication of information be justified. This ethical approach is the most effective way to manage the conditions of risk. A certain consensus exists in pharmacovigilance in considering that the most appropriate procedure involves health professionals as the primary receptors of information, which makes it possible for them to act as a reference for potentially affected individuals. Only after this first phase should news of the risk, if necessary, be disseminated to the population, either through mass media or other procedures.

It is important to distinguish two different situations: a known risk and an emerging risk.

The first should be part of the daily clinical practice routine. As a standard, the information should be as complete as possible, within the patient's ability of taking on, starting naturally from some minimums that include risks considered to be preventable and the serious unexpected risks. Complementary written information, especially when a genuine patient-directed prospect does not exist, can be a great help in this effort.

With respect to the second situation, an emerging risk, the most appropriate channel for informing citizens has been debated so that subsequent decisions can be made without creating unnecessary panic or social alarm; currently, however, no universal guidelines have been adopted that serve as orientation and that help avoid improvisations; the subject is still pending for the majority of drug regulatory authorities.

The adopted measures will be disseminated through appropriate communication channels, such as:

- Officially established labeling (primary container, secondary container, interior or prospective literature, informative sheet or monograph and summary of product features)
- Letter of response to complaints and claims
- Risk communications aimed at health professionals
- Resolutions of health measures to reduce risk
- Bulletins available through print, e-mail, or on the Internet.
- Scientific articles
- Public warnings in mass media (press, radio, television, Internet)

5.6.2 Crisis Management

A crisis can occur when new information is made available on the safety or efficacy of a product that can have a significant impact on public health and that accordingly requires actions immediate. A crisis also can also arise when bulletins are disseminated in the mass media, in which a certain concern about a given product is stated.

When a crisis occurs, the regulatory agency should analyze the available information and use it to make pertinent decisions. These can be regulatory measures, to seek or generate more information and always to communicate the risk in the absence of such information. In any case, the involved parties should always cooperate closely and have the capacity to take urgent actions, when there is evidence of risk and significant impact on public health.¹⁴

If the crisis occurs, the regulatory drug agency should take certain actions in order to adequately channel the information:

- Put the involved parties in touch.
- Insofar as possible coordinate with the stakeholders in order to have a consensus on the subject and its application at the local level.
- Agree with the stakeholders on a single bulletin for the public, including patients and health workers; if this is not possible, the health authority will publicize its position to address the problem.

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

- 1) Confirmation of the crisis
- 2) If considered necessary, initiate the process of management
- 3) Rapid scientific determination of the risk/benefit of the crisis
- 4) Definition of the strategy to follow
- 5) Recommendations on the need for action, in accordance with the available reports by the involved parties
- 6) In the event that the regulatory agency determines that actions should be taken, these should be monitored
- 7) Development of an action plan, and monitoring of such plan

In any case, the agency should establish a communication mechanism with the media and the press to give timely information that avoids speculations and helps manage the crisis from the safe perspective of the agency.

5.7 Risk Prevention

Preventive strategies should be designed, since a significant number of adverse events arise from errors in practice of utilization and preventable adverse reactions (!!).

Risk prevention should be carried out routinely. Health professionals (physicians, dentists, pharmacists, nurses), consumers, companies, and health authorities have shared responsibility. Communication among these actors plays a key role in routine prevention. Intensive pharmacovigilance programs or monitoring

programs can also be developed for given drugs (clozapine, for example) or risk groups (e.g., pregnant women, children, the elderly). In terms of **unavoidable** adverse reactions, early detection should be the goal, i.e., a preventive measure to reduce the magnitude of harm. Information for both health professionals and patients without a doubt constitutes the best strategy.

5.8 Evaluation of the Pharmacovigilance System

Evaluation should be built within the monitoring system. The coordinating and reviewing national center should periodically evaluate the operation of the system, if present and to what degree:

- The reports are complete, on time and accurate;
- The response have been rapid;
- Management of the cases has been appropriate; and
- If the action has been appropriate in order to avoid errors.

Ideally, certain criteria for evaluating the system should be determined, such as:

- Distribution of the reports by professional, specialization, or patient category.
- Quality of reports: complete information, accuracy of description, value of the contribution for decision-making.
- Number of reports describing serious or unknown reactions.
- Timeliness of the report.
- Index of report, such as the number of cases reported per unit of population or per number of health workers.
- Assessment of impact of adverse reactions on morbidity, mortality, and costs in health (usually measured by hospital admissions due to adverse reactions).

As mentioned in the WHO document, World Partnership for Patient Safety,¹ the **characteristics of a successful reporting system** are described:

<i>Non-punitive</i>	The reporters are free of fear of being punished or receiving reprisals due to the report
<i>Confidential</i>	The identity of patients, reporters, and institutions are never revealed.
<i>Independent</i>	The reporting system is independent of any authority with power to punish to the reporter or the institution.
<i>Expert analysis</i>	The reports are evaluated by experts who understand the clinical circumstances and are trained to recognize the underlying causes in the system.
<i>Immediate action</i>	The reports are quickly analyzed and recommendations disseminated rapidly to those who need to know them, especially when serious dangers are identified.

Guided systems

Recommendations focus on changes to the systems, processes and/or products more than on individual development.

Responses

The agency that receives the report is capable of disseminating recommendations.

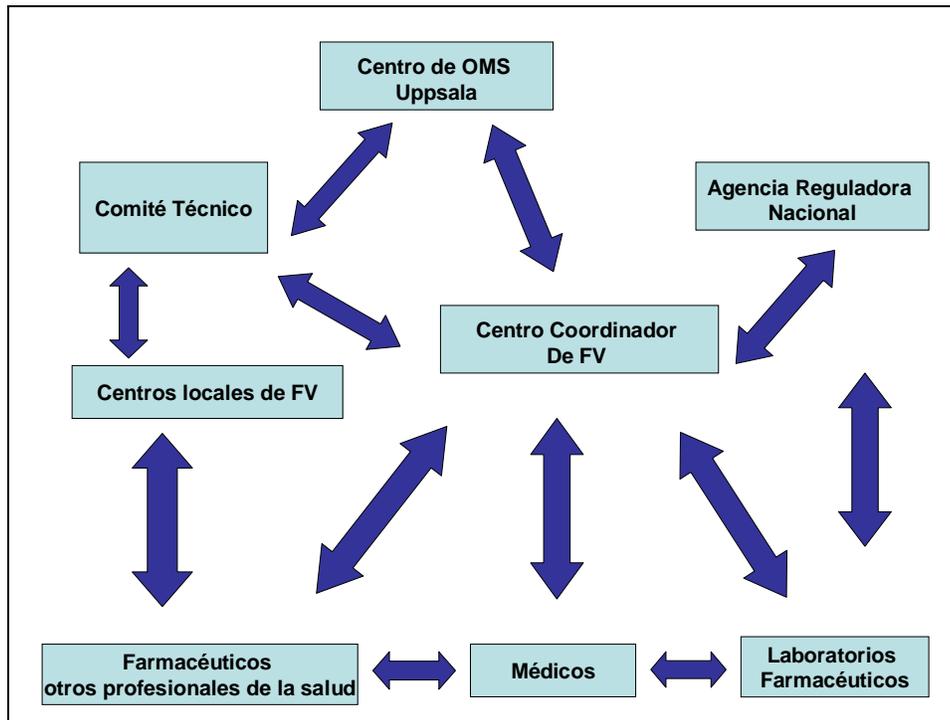
6. DUTIES AND RESPONSIBILITIES OF AGENTS INVOLVED

Pharmacovigilance is a cooperative work and an activity of shared responsibility among all the agents or actors involved with drugs: health authorities, pharmaceutical laboratories or licensed manufacturers, hospitals and universities, medical and pharmaceutical associations, nongovernmental organizations, information centers on toxic products and drugs, health professionals, patients, consumers, and communications media. To attain coherent development and prevent unnecessary or duplicated responsibilities, effective collaboration, coordination, communication, and public relations among all these actors are necessary.

In this guide we will define the objectives, duties, and interrelationships of the principal agents or actors:

- National regulatory authority
- National pharmacovigilance systems
- Health professionals
- Pharmaceutical laboratories or licensed manufacturers
- Other health institutions

The following diagram shows the relations between the agents in a pharmacovigilance system; however, other inter-relational models also exist.



6.1 NATIONAL REGULATORY AUTHORITY

It is the responsibility of national governments to safeguard the supply of safe, effective, and quality drugs, and their correct use. The agency responsible for public health should know about the risks of adverse reactions, their diagnosis, reporting, and management. Government resources are necessary for national coordination of pharmacovigilance. As previously mentioned, multidisciplinary collaboration takes on great importance, and it is especially important that the health authority forges the necessary ties among the various departments of the ministry of health and other relevant sectors that intervene in the rational use of drugs and pharmacotherapy control.

Essential elements

In order to satisfactorily perform those functions, the agency responsible for public health needs to:

- Create or use (if it already exists) a national drug regulatory organization, in this document called ***national regulatory authority*** that prepares legislation and/or regulations on the control of drugs. This also includes medical equipment or products, herbs, diagnostic reactions that could affect human health.
- Develop **national policies and action plans**.
- Create a ***national pharmacovigilance system***.
- Designate and/or create an official **national or coordinating center** to study adverse reactions.

The national drug regulatory authority should have an advisory committee, or a **safety committee on drugs for human consumption**, to analyze and evaluate the available evidence, research findings, and reports on adverse drug events, in support of decision-making.

Essential elements for pharmacovigilance activities in a country – always in alliance with a national policy on drugs, and for the purpose of meeting public health goals – include:

- Rational and safe use of drugs on the part of health professionals;
- Evaluations and communications of the risks and effectiveness of the drugs used; and
- Education and information for patients and health professionals

The national regulatory authority in each country should have the commitment and potential to react to the signs that arise from the national pharmacovigilance systems and/or centers and to take the appropriate regulatory measures. It should also monitor the impact of the system's or center's activities through process and outcome indicators. Continuous information on adverse reactions should also be provided to professionals and consumers, as well as ongoing education for health professionals.

The regulatory authority's mission is to protect health, through monitoring the relative safety and effectiveness of the products designed to protect and reestablish health. This includes not only drugs and food, but also cosmetics, diagnostic reagents and all sorts of medical equipment and products for domestic use that could affect health.

Activities

For drugs approved by the national drug regulatory authority, the authority should ensure that the following activities are carried out in accordance with current legislation:²⁷

- Report and manage suspected adverse reactions.
- Prepare and/or review periodic reports on safety.
- Respond quickly and thoroughly to any request for information from the responsible authorities on drug safety.
- Continuously evaluate the benefit/risk balance during the post-approval period and immediately communicate with the responsible authorities on any information that could imply a change in such relation
- Establish criteria for identifying and assessing the severity of signs and signals
- Supervise post-approval studies on safety
- Periodically review the scientific literature on spontaneous adverse reactions to the active ingredients licensed by the manufacturer or industry
- Cooperate with the pharmacovigilance centers on drug safety issues.

Relation with the licensed manufacturers

²⁷ Good practices in drug monitoring, Generalitat de Catalunya Departament de Sanitat i Seguretat Social Direcció General de Recursos Sanitaris. Online. < <http://www.gencat.cat/salut/depsalut/pdf/esbpfarvig01cas.pdf> > [accessed in September 2008]

The drug regulatory authority will confirm that the pharmaceutical and/or licensed manufacturing laboratories have monitoring and research programs for marketed drugs.

The pharmaceutical and/or licensed manufacturing laboratories should be required to make available all relevant information on the profit/risk balance of any of their products in a timely and thorough fashion in accordance with the regulatory framework.

The drug regulatory authority will confirm that the pharmacovigilance activities of the pharmaceutical and licensed laboratories are performed by trained staff.

The national regulatory authority will establish pertinent inspection procedures that ensure the fulfillment of the duties of the licensed manufacturers indicated in the laboratory's responsibilities, and thus can audit pharmacovigilance departments in pharmaceutical labs and/or licensed manufacturers and determine their quality, suitability and operations.

Furthermore, the regulatory authority will determine the need for and request any corrective measure, structural modification, or sanction, as needed, in accordance with current regulations.

Certification of good pharmacovigilance practices for the pharmaceutical industry

The certificate of guarantee of good practices in pharmacovigilance should be issued by the national regulatory authority. The authority will certify that pharmaceutical companies:

- Implement pharmacovigilance programs that effectively meet the regulations and adhere to the guidelines of good practices in pharmacovigilance established in the present document.
- Attend and participate actively in the health authority's training programs.
- Show through its reports to the authority that pharmacovigilance activities are being carried out within quality parameters.

Those institutions with pharmacovigilance programs previously endorsed by international health authorities (FDA, EMEA) are automatically certified, although they will have to attend the activities programmed by their local health authority.

6.2 National Pharmacovigilance System.

The pharmacovigilance systems will collect, analyze, and distribute information on adverse reactions, recommending measures that should be adopted.⁶ These act as **central agents**, receiving the reports from peripheral agents, health professionals, or drug consumers. They evaluate the reports and rank the information received to formulate recommendations to the sectors involved in the health system, on the risks and/or detected benefits of a drug, and all the pharmacological, therapeutic and toxicological information they have evaluated and considered for dissemination. A pharmacovigilance system should be supported by the regulatory agency as mentioned in item 6.1.

The specific needs of each country's system will differ in accordance with the pharmacovigilance initiatives. The efforts required will depend on the existing systems and infrastructures in each country. Some countries have well-established national pharmacovigilance centers already in operation, backed by a

national regulatory authority. In such countries there is a public health department with an initiative vertically related to a specific health program. In other countries, the public health department can use the same center that runs different disease programs and the pharmacovigilance centers may be rudimentary, and in other cases, absent.

In order to organize a pharmacovigilance system, there should be a clear sense of the questions that need to be addressed before implementing the work plan (!!!). Only with clear goals can collection of appropriate data and an analysis plan be implemented.⁸ The strengths should be based on the development of new methods for evaluating drug safety, including active studies, better analysis of data and of the sign processes of detection. Another strength of these systems of considerable importance for public health is the training and expertise in evaluation of effectiveness/risk and its communication to the population, an essential component of the good practices in pharmacovigilance and an ethical imperative.²⁸

On the functional requirements, they will range between the countries and they will depend on health systems and regulatory authority of each country. But it is essential to produce clear organization charts specifying roles and responsibilities of the personnel, physical location, and the precise level of responsibilities (national example, state, district, primary health centers and others).

Pharmacovigilance systems have the following functions:

- i. Plan, coordinate, evaluate, and develop pharmacovigilance throughout the entire national territory.
- ii. Establish a coordinating or national pharmacovigilance center to perform these main functions: report, collect data, coordinate, investigate, and manage the adverse reactions in the country.
- iii. Manage the database, evaluate the causality and data analysis.
- iv. Promote the formation of a National Commission on Safety of Drugs For Human Consumption.
- v. Coordinate decision-making with on the risks and/or safety related to drug use.
- vi. Promote good practices in pharmacovigilance at the different organizational levels and in the national territory.
- vii. Coordinate with regulatory activities.
- viii. Train health professionals to report adverse reactions and in all aspects of pharmacovigilance.
- ix. Promote pharmacovigilance activities.
- x. Be the international link with other countries and international centers.

6.2.1. National Pharmacovigilance Centers

²⁸ Effective communications in drug monitoring containing The Erice Declaration on communicating medicine safety information. Uppsala, Sweden, Uppsala Monitoring Centre, 1998.

Drug monitoring systems are implemented through national centers, and responsibilities include:

- Act as reference center with regard to monitoring drugs for human consumption in the country.
- Receive, evaluate, code and upload in the pharmacovigilance database the reports on suspected adverse reactions and problems related to drugs that are sent by the pharmaceutical or licensed laboratories of the registry of marketing of you drugs.
- Monitor the safety and confidentiality of data and their integrity during the data transferring processes.
- Coordinate activities of each pharmacovigilance center in the country within established standards.
- Act as spokesperson of the national pharmacovigilance system with the pharmaceutical industry, pharmaceutical laboratories, or licensed manufacturer of drugs for human consumption.
- Care that all reports of suspected serious adverse reactions in national territory are recorded and communicated as soon as possible.
- Administer the national pharmacovigilance system database, continuously ensuring its availability and updating.
- Ensure the quality of the database.
- Develop methods for obtaining early warning signals.
- Coordinate the monitoring of publications of locally occurring adverse reactions and published in national or international medical journals.
- Ensure the data of the collected reports, whether it is in accordance with these Good Practices of Pharmacovigilance, and avoid to the utmost the existence of duplicated reports.
- A new pharmacovigilance center should establish contact with the World Health Organization in Geneva, Switzerland, and the Uppsala Monitoring Center (UMC). It is useful to establish contacts with national pharmacovigilance centers in neighboring countries. If these countries have more experience, their collaboration will be useful in training new personnel.
- Act as national reference center in the WHO international pharmacovigilance system, periodically sending (at least every two months) the adverse reactions and participate in the meetings organized by WHO on pharmacovigilance issues.
- Transmit any urgent regulatory measure due to a safety problem to the therapeutic committees, and to all responsible agencies as provided for in the procedures on communication of risks.
- Conduct studies to evaluate the safety of drugs for human consumption.
- Promote the information and formation of pharmacovigilance in all health services of the country.
- Instruct the procedures derived from the infractions related to the monitoring of the drugs when it corresponds.
- It should assume the categories of coding and the terminologies adopted in international forums of regulatory character (such as the international conferences on harmonization).
- Implement the return of report results to the reporters (health professionals), since they are the pillars of the reporting system.

6.2.2. Local Pharmacovigilance Centers

Local centers or peripheral actors may be independent or of spontaneous origin, but must report to national centers. Responsibilities include:

- Implement, develop, and strengthen in its territorial scope the Spontaneous Notification System, as well as other programs, in accordance with the Good Practices of Pharmacovigilance.
- Receive, evaluate and process the locally occurring cases of suspected adverse reactions, communicated by health professionals or the pharmaceutical industry, as well as from the scientific bibliography and post-authorization studies, when applicable.
- Suspected serious adverse reactions should be sent to the coordinating center in the national pharmacovigilance system's database within the maximum time limit of ten calendar days from their reception.
- Publish and distribute suspected adverse reaction cards (yellow card) and drug-related problems to health professionals in their geographical area.
- Document and validate information on reports of suspected adverse reactions to the degree possible, confirming its authenticity and coherence with available original documents.
- Maintain the reliability of the data on reports of suspected adverse reactions, using terminology similar to that used by the reporter.
- Maintain the confidentiality of the personal data on the patient and the reporter.
- Respond or return in time and form of the reports to the professionals who reported them, to promote their participation.
- File and safely store all reports collected on suspected adverse reactions.
- Implement methods for obtaining early signs or alert.
- Contribute to the scientific progress improving drug monitoring methods, as well as the knowledge and the comprehension of nature and mechanisms of adverse reactions adverse to drugs.
- Respond to the requests for information on adverse reactions from health professionals in their geographical area. Keep a record of both the requests and responses provided.
- Respond to requests for information from the health authorities.
- Promote and participate in the education of health professionals on pharmacovigilance.
- Participate in the meetings of the national pharmacovigilance system.
- Establish an internal system of quality assurance that ensures adherence to good practices in drug monitoring.

6.3. Health Professionals

The effectiveness of a national pharmacovigilance system depends directly on the active participation of health professionals. They are in the best position to report any suspected adverse reactions observed in patients during the daily practice. All medical health professionals, pharmacists, nurses, dentists, and

others should report adverse reactions as part of their professional responsibility, even if they are in doubt about the precise relationship with the medication.²⁹

Originally, physicians were the only ones asked to report adverse events, based on their skill of differential diagnosis to identify whether the symptoms are due to drugs or to disease. Also, it was argued that data exclusively from doctors would ensure high quality and minimize the reporting of unrelated associations.

Studies have shown, however, that in order to detect a wider range of adverse reactions, all health practitioners must be involved. All sectors of health care should participate: public and private hospitals, primary care centers, dispensaries and clinics, doctors' offices, pharmacies, and vaccination centers. Health personnel who work in these places can provide a representative picture of reality.

Health professionals' responsibilities include the following:

- Report all suspected serious or unexpected adverse reactions and all those of recently marketed drugs, as well as drug-used-related problems.
- Send such information as soon as possible to the respective local or national center, through the yellow card spontaneous report scheme used by the national pharmacovigilance system.
- Conserve clinical documentation on adverse drug reactions, for the purpose of completing or performing monitoring, if necessary.
- Cooperate with the technicians in the national pharmacovigilance system, providing the necessary source documents, as requested, in order to provide expanded or complete information on the reported cases of suspected adverse reactions.
- Keep informed on latest information on the relative safety of regularly prescribed, dispensed, or administered drugs.
- Collaborate (through contributing information) with those responsible for pharmacovigilance in the pharmaceutical laboratories or licensed manufacturers, when requested, upon learning of the existence of an adverse reaction in a patient who has used a drug.

In cases where adverse reactions are reported directly by patients to a national or local center, it is useful to have the possibility of communication with their physicians in order to gather more information and confirm the data.

6.4. Pharmaceutical Laboratory or Licensed Manufacturer

The manufacturing pharmaceutical laboratory or licensed drug manufacturer is legally responsible for the safety of its drugs. This should ensure that the suspected adverse reactions to their drugs are reported to the country's responsible authority.

²⁹ Safety of Medicines. A guide to detecting and reporting adverse drug reactions. Why health professionals need to take action World Health Organization Geneva 2002 WHO/EDM/QSM/2002.2 Original: English.

The manufacturing pharmaceutical laboratory or licensed drug manufacturer should have an adequate pharmacovigilance system so that it can assume its responsibilities and obligations of the drugs that it authorized to market, and ensure the adoption of appropriate measures when necessary. Although in each country the national regulatory authority's responsibilities should be specified, its basic obligations are:

- Report, through the pharmacovigilance system, all suspected serious adverse reactions received from a health professional, within the time frame defined by the authority in each country. In general, it is fifteen days following receipt.
- Keep detailed record of all suspected adverse reactions that have been observed and reported to the national regulatory authority.
- Designate a qualified professional to be permanently and consistently responsible for the tasks of pharmacovigilance, facilitating the suitable means for fulfilling the functions, who will act as point of contact with the regulatory authority.
- Propose timely modifications in the technical file, when unexpected adverse reactions are produced in the file.
- Ensure that all laboratory staff receive training specific to their responsibilities in pharmacovigilance.
- Transfer some or all of the duties and responsibilities to another company, but not the ultimate responsibility of monitoring brand name drugs.
- Establish agreements on pharmacovigilance issues, in the scenario of joint marketing agreements between several companies. Any transfer of pharmacovigilance duties and responsibilities should be documented through a written agreement signed by representatives of the two companies. The functions not transferred through this agreement continue to be assumed by the licensed manufacturer. Such transfers of duties and responsibilities need to be reported to the corresponding health authorities.
- Facilitate the designated professional's access to the information sheet and basic safety information of each approved pharmaceutical product, appropriately up-to-date.
- Ensure that appropriate standardized work procedures are established and followed.
- Guarantee a filing system that helps conserve all the documentation related to the responsibilities and activities of pharmacovigilance. The responsibilities for file management have to be defined in writing.
- Establish an auditing program to help ensure that the pharmacovigilance system adapts good practices.
- It is recommended that the designated professional be the only valid spokesperson on pharmacovigilance before the competent health authorities. The name of this professional should be provided to the competent health authorities, as well as any changes that may occur.

6.5. Other Health Institutions

The growing body of scientific knowledge on drug safety is due to growing academic awareness and interest. Efforts made by the clinical pharmacology and pharmacy departments throughout the world have helped develop pharmacovigilance as a clinical discipline. Pharmacology and pharmacy departments in

hospitals and universities have played an important role through teaching, training, policy development, clinical research, ethics committees, and clinical services.

6.5.1. Hospitals and Other In-patient Centers

Adverse drug reactions that lead to admission in hospitals or extended stays have greater impact on health and the economy; however, there is a marked underreporting of adverse reactions partly due to the low participation many professionals in hospitals and in-patient facilities in reporting them.

Hospitals constitute centers of great importance for pharmacovigilance work due to the high incidence of fatal adverse reactions and hospital admissions, as shown in various international studies.

Pharmacovigilance work in hospitals will be centered by the pharmacoepidemiology of the hospital and in its absence by the technical director of the hospital's pharmacy, whose main responsibilities will include:

- Distribute the report forms to all health professionals in the hospital.
- Receive, assess, and process reports of suspected adverse reactions submitted by health professionals in the hospital.
- Complement with the reporter, the information that is not available, and is necessary for delving further into the search for a possible sign or alert.
- Identify the valid reports and submit them to the coordinating center, discarding the invalid one.
- Send the reports on fatal or serious cases occurring in the hospital to the coordinating center within 24 hours.
- Maintain the confidentiality of personal data on the patient and reporter.
- Review and purify the reports received to avoid duplication.
- Deepen and review the scientific literature available in the field of adverse reactions.
- Propose and develop pharmacoepidemiological studies in the hospital, in order to evaluate the safety profile of drugs
- Respond to requests for information on adverse reactions from professionals of the hospital.
- Promote and participate in educating health professionals and technical personnel on pharmacovigilance and pharmacoepidemiology of the hospital.
- Respect the standards and procedures established by the country's health authority.
- Provide feedback to the reporters.

6.5.2. Universities

An important aspect of pharmacovigilance is educating health professionals, both in graduate and post-graduate degrees. Appropriate educational activities can improve their knowledge and understanding of adverse drug reactions and motivate reporting.

Pharmacovigilance studies should be included in the undergraduate curriculum of careers in medicine, pharmacy, dentistry, and nursing.

Pharmacovigilance centers can contribute to and participate in post-graduate programs. The hypotheses or findings of the pharmacovigilance system can stimulate potential interest in conducting additional studies on mechanisms, frequency of reactions, and other aspects. These can be utilized by epidemiology or pharmacology departments at universities and institutions.¹²

The implementation of a pharmacovigilance system is always strengthened by partnerships with pharmaceutical laboratories, academia, and the regulatory activities, with great implication for pharmacovigilance development.³

6.5.3. Drug and Toxicology Information Centers

Drug and toxicology information centers have a lot in common with pharmacovigilance centers, in both organizational and scientific aspects. If pharmacovigilance is initiated in a country where a toxicology center or a drug information center already exists, it is good to collaborate closely with them. Expensive installations – such as secretarial services and computer and library resources – can be shared. In any case, collaboration is a desirable objective.

In turn, drug information centers and local or national committees can benefit from collaboration with the pharmacovigilance center.

6.5.4. Safety Committee on Drugs for Human Consumption

Usually, there are collegiate bodies that advise the national drug regulatory authority and allied associations on drug safety issues.

The committee evaluates safety problems that arise with marketed drugs and proposes measures aimed at reducing the detected risk. The composition of the committee can be flexible and as much as possible incorporate prominent professionals from the national network, academia and international pharmacovigilance groups, acting in accordance with a statute.

A spokesperson is designated for each subject (an expert who may be a committee member or not) who prepares an evaluation report and presents it for discussion. As established in the statute, when the committee recommends making a substantial modification, revocation, or suspension of the marketing license for a brand name drug, it is its responsibility to report officially to the interested pharmaceutical laboratory on its right to an audience before the Committee. In the event that the pharmaceutical laboratory wishes to exert this right, a meeting with the Committee is convened, where an oral presentation on the matter of debate is made. Any agreements reached within the Committee will be adopted by the management of the drug regulatory authority, and the pharmaceutical laboratories affected by the decisions will be notified in writing.

Committee responsibilities include:

- Evaluate the benefit/risk relation of drugs due to safety problems (this is the Committee's main responsibility, among others).
- Propose studies and research on pharmacovigilance issues.
- Collaborate in coordinating, planning, and developing the pharmacovigilance system in the evaluation of post-approval studies.
- Provide technical assistance to national regulatory authority representatives who attend PAHO working groups and meetings on pharmacovigilance issues.

6.5.5. Professional Associations of Physicians and Pharmacists

Many associations, including medical or pharmaceutical associations, implement monitoring systems to follow adverse reactions and errors in medication. These associations provide current information from their fields and can also offer infrastructure that facilitates studies and personnel training.

6.5.6. Consumer Organizations and the Media

Support from national consumer organizations and patients rights groups can help the general acceptance of pharmacovigilance, promote reporting of incidences, and defend patients rights.

Good relations with leading journalists can be very useful, for example, for general public relations and as part of a risk management strategy, in any moment that an acute drug problem arises. A special precaution should be made in explaining the limitations of pharmacovigilance information to journalists (see 5.6 Communication of risks).

7. PHARMACOVIGILANCE PUBLICATIONS

Publication and dissemination is an important aspect that should not be forestalled; the information obtained and evaluated should be publicized through the appropriate channels:

- Information on suspected adverse reactions should be immediately disseminated through publications, either health professionals, licensed manufacturers, established monitoring systems, or other institutions and drug regulatory authorities.
- Before publication, the pertinent institutions and the drug regulatory authority should be notified, through the established methods, on serious and unexpected reactions; also, the company responsible for marketing the involved drug should be notified.
- Those responsible for publishing should have access to all the elements that allow the authenticity of data to be ensured.
- The title of the publication should indicate the adverse reaction and the suspected drugs.

- Elements should be included in the publications that help optimally evaluate the observation, taking into account the characteristics and number of observations reported and the existence of previously reported cases in the biomedical literature, as established.

Special attention should be paid to the following information:

- Description of the characteristics of the involved subject: gender, age, background, and current diseases
- Description of the supposed adverse reaction: date of onset, clinical and biological parameters of the diagnosis, evolution and duration, the degree of severity evaluated according to international criteria
- Description of the suspected drugs and simultaneous treatments: international generic name, name of the brand name drug, dosage form, indications, dosages, dates of onset, and the end of the treatment, if applicable
- Data that helps in evaluating the causal relation: treatment duration, effect of discontinuation and eventual re-exposure to the suspicious drug, clinical or biological data that might help explain the possible role of the suspected drug
- Elements that help exclude the non-pharmacological etiology
- Annex, if any, similar cases published in the literature, to help evaluate the originality of the observation.

The absence of one or more of the above-mentioned elements will be accepted in the cases of serious and unexpected reactions, whenever justified.

The publication of series of cases will allow the same analysis as for individual cases. If there are too many cases to give a detailed description of each observation, the most important data will be presented in the form of tables (age, gender, treatment duration, nature of adverse reaction, evolution after discontinuation of treatment), while the rest of the above-mentioned information will be available at the request of the publishers.

In this case, observations that help establish a causal relation and identify risk factors will be emphasized; to report on, insofar as possible, the number of cases with data on consumption of the suspected drug, indicating the source of the information.

Justify the precise wording of the title, in particular the possible causal relation and conclusions based on the reported data and a rigorous discussion.

7.1. Publisher Participation

The editors have the responsibility to:

- Favor the timely publication of the serious adverse reactions as well as unexpected adverse reactions.
- Guarantee that prior to the acceptance, they have notified the corresponding institutions and health authority, requesting a verification letter or acknowledgment of receipt.
- Submit the publications to a review committee with a pharmacovigilance expert.
- Communicate the project of the publication to those responsible for marketing the involved drugs, and offer the chance of publishing their eventual responses to the publication, if the arguments they present are rigorously justified.
- Request that the review or drafting committee carry out pertinent verifications, to guarantee the quality of information in the publication.

7.2. Guidelines for Editors and Authors when Publishing Information on Adverse Reactions.

Initial reports on an observation:

- Will be presented as unreviewed suspicions, different from the following (b).
- Its importance lies in the degree of novelty.

Reporting on reviewed cases: the general information necessary for an external review, acceptance, and publication in the journal:

- Age or date of birth, gender
- Suspicious drug and other drugs administered at the same time, with data on date of onset, discontinuation, and re-initiation, with dosage and type of administration
- Therapeutic indication justifying its use
- Chronological sequence between the event (suspected ADR) and administration of the drug (and consequences)
- Other relevant diseases/environmental factors and their corresponding dates
- Patient's prior experience with this drug or ADR history with other similar drugs
- Additional information from the manufacturer or regulatory authority
- Previous publications on the same case, of any length
- Other relevant factors to confirm some specific types of ADR (for example, blood levels in particular in overdoses, laboratory data, histology, ethnic origin, etc.)

7.3. Publications on Series of Multiple Cases.

Any communication on a series of cases should include data on:

- Age, gender
- Number of patients treated
- Number of patients with ADR
- Number of each type of ADR
- Information on previous publications

- Other relevant factors to confirm the specific types of ADR

5. GLOSSARY OF TERMS USED IN PHARMACOVIGILANCE

Abuse Deliberate excessive, permanent, or sporadic use of a drug that it is accompanied by harmful physical or psychological effects.³⁰

Adulterated drug An adulterated drug is considered for legal and regulatory purposes to be: a drug that does not have the same definition or identity as that attributed by the official or reference pharmacopeia with regard to its physical-chemical qualities; a drug that does not have the same identity, purity, potency, and safety as the name and qualities announced in its labeling; a drug that is sold in packaging or wrapping that are not allowed by regulations since it is considered that hazardous substances can be added to the drug or react with the drug in a way that changes its properties; a drug that contains color or other additives considered to be technically hazardous for this particular type of drugs; a drug that has been manufactured, handled, or stored in unauthorized conditions or in conditions that do not comply with regulations.³⁴

Adulteration Condition in which the contents or nature of a drug, biological, medical device, or dietary supplement are the result of a manufacturing process that does not comply with Good Manufacturing Practices.³¹

Adverse drug reaction (ADR) According to WHO, "a harmful and undesirable reaction that occurs after administration of a drug, 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 drug administration and 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-effect relationship. It should also be noted that this definition excludes poisoning or overdoses. Response to a drug that it is harmful and unintentional, and occurs with the doses usually used in humans. In this description 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 "adverse drug reaction") Synonym of adverse reaction and undesirable effect.³¹

³⁰ De la Cuesta M V, Palop R, Ayani I. Buenas Prácticas de Farmacovigilancia del Sistema Español de Farmacovigilancia. Ministerio de Sanidad y Consumo. Centro de Publicaciones. Madrid. 2000; 2: 9-17.

³¹ Términos Utilizados en Investigación Clínica. En: Laporte J-R. Principios Básicos de Investigación Clínica. 2ª ed Astra-Zeneca, 2001. En línea <<http://www.icf.uab.es/livre/Libre.htm>> [acceso mayo 2008].

Adverse event Any unfortunate medical event that can occur during treatment with a drug 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) This is the database of the computerized FDA adverse event reporting system designed to confirm the safety evaluations of the post-marketing programs for all approved drugs and biologicals.¹²

Adverse incident (AI) An adverse incident is an injury or potential risk of unintentional injury to the patient, operator, or environment that occurs as a result of use of a medical device or apparatus (see “medical device vigilance”).³⁸

Alert or sign Information reported about a possible causal relationship between an adverse event and a drug when this relationship was previously unknown or not completely documented. Usually more than one report is required in order to produce a sign, depending on the severity of the event and the quality of the information.³¹

Algorithm Systematized decision-making process that consists of an orderly sequence of steps in which each of the steps depends on the result of the previous step. The use of algorithms to make clinical decisions tends to reduce inter-observer variability.³²

Allergic drug reaction An adverse drug reaction that is dose-dependent and is mediated by the immune system. Allergic reactions have been classified into four main clinical types:

Type 1, known as immediate anaphylactoid or hypersensitivity reaction, is mediated by interaction of the allergen (drug) and IgE antibodies. Reactions caused by administration of penicillin are an example of this type of reaction.

Type 2, or cytotoxic reactions, are complement fixation reactions between the antigen and an antibody present on the surface of some cells. These reactions include drug-induced hemolytic anemia, agranulocytosis, and other reactions.

Type 3, reactions mediated by an immune complex deposited on the cells of the target organ or tissue.

Type 4 results from direct interaction between the allergen (drug) and the sensitized lymphocytes. It is also known as delayed allergic reaction and includes contact dermatitis.¹³

Alternative cause In assessment of the causality relationship, when there is an explanation, underlying condition, or another drug taken at the same time which is more likely than the causal relationship with the drug studied.³²

Analytical study A study designed to examine associations, the final purpose of which is usually to identify or measure the effects of risk factors or specific health interventions. Analytical studies can be controlled clinical trials, cohort studies, case-control studies, or cross-sectional studies.³¹

Anatomical, therapeutic, and chemical classification (ATC) System of coding drugs 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 of the groups in the first level is subdivided into four more levels; the second and third level are pharmacological and therapeutic subgroups; the fourth level refers to the therapeutic/pharmacological/chemical subgroups, and the fifth level designates each drug.³²

Beneficial Effect of a therapeutic intervention that is considered advantageous for the patient. Beneficial effects may have been sought or be unexpected.³¹

Benefit This is usually stated as the proven therapeutic effect of a product, although it should also include the patient's subjective evaluation of such effects.³³

Bias Systematic shift of all observations obtained about a sample with regard to the real or accepted value. It is also used to refer to a systematic or constant error in test results or an influence on sample selection that make the sample unrepresentative with regard to a given variable.³⁶

Bioethics Clinical research ethics. For a clinical trial or another study to be ethical, the following must occur: (1) reasons to question which is the strategy with the most favorable (*equipoise*) risk/benefit relationship or, in the event that a treatment is only being tested, to presume that its benefits are greater than its risks; (2) proper design and qualified investigators; (3) participants are fully aware of the consequences and freely and voluntarily participate. According to by D. Gracia, the four basic bioethical principles are respect for people, beneficial effects, justice (stated in the Belmont Report), and lack of harmful effects.³²

Biological Medical product prepared based on biological material of human, animal, or microbiological origin (e.g., blood products, vaccines, insulin).³¹

Biological plausibility In assessment of causal relations in epidemiology, when the association found agrees with the experimental biological knowledge available.³¹

³² Normas y procedimientos de trabajo del sistema cubano de farmacovigilancia. Unidad coordinadora nacional de farmacovigilancia. Cuba 2006.

³³ Arias TD. Glosario de Medicamentos: Desarrollo, evaluación y uso. Organización Panamericana de la Salud. Washington D.C. OPS c1999.

Case-control study A study in which persons with a certain disease or symptom (cases) are compared to other persons that do not have the disease or symptom studied (controls) with regard to prior exposure to risk factors. Such studies are, by definition, retrospective studies. In a case-control study a single disease is studied, but several risk factors or exposures are considered.³¹

Causality (see also “imputability”) The causality categories can be defined based on the result of the imputability analysis and individual evaluation of the relationship between drug administration and onset of an adverse reaction.¹²

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

- **Certain:** a clinical event, including abnormal laboratory tests, that occurs within a plausible time sequence with regard to drug administration and cannot be attributed to a concurrent condition or to other drugs or substances. The response to discontinuation (withdrawal) of the drug should be clinically plausible. The event should be certain from a pharmacological or phenomenological viewpoint, and a conclusive re-exposure procedure should be used if necessary.
- **Probable:** a clinical event, including abnormal laboratory tests, that occurs within a reasonable time sequence with regard to drug administration, it is unlikely that it can be attributed to a concurrent condition or to other drugs or substances, and in which a clinically reasonable response occurs when the drug is withdrawn. Information about re-exposure is not required in order to assign this definition.
- **Possible:** a clinical event, including abnormal laboratory tests, that occurs within a reasonable time sequence with regard to drug administration but can also be attributed to a concurrent condition or to other drugs or substances. Information about drug withdrawal may be missing or may be unclear.
- **Unlikely:** a clinical event, including abnormal laboratory tests, that occurs within an improbable time sequence with regard to drug administration and can be more plausibly attributed to a concurrent condition or to other drugs or substances.
- **Conditional/Unclassified:** a clinical event, including abnormal laboratory tests, reported as an adverse reaction, in which additional data is required in order to make a suitable assessment or such data is being examined.
- **Unassessable/Unclassifiable:** a report that suggests an adverse reaction but cannot be evaluated because the information is insufficient or contradictory and the data cannot be confirmed or verified.¹²

Clinical significance Probability that a difference observed will have an impact on the progression of the problem or disease treated that it 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 occur often.³¹

Cohort study A study in which persons that undergo a certain exposure or treatment are compared to persons that 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 of a prospective study. In a cohort study, a single drug or group of drugs is studied, but several diseases are considered.³¹

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 required precautions must be taken in order to ensure data safety and confidentiality, as well as its integrity during the data processing and transfer processes.³⁰

Confounding factor A variable that is independently associated with the risk factor and the disease studied at the same point in time and can change the outcome of the study. Such variables should be identified and their influence should be avoided. Therefore, for example, in a study that aims to evaluate the relationship between use of oral antidiabetics during pregnancy and potential for increased risk of birth defects, diabetes would be a confounding factor because it is associated with 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 analytical phase by stratification and multiple regression analysis.³¹

Coordinating pharmacovigilance center National reference center on pharmacovigilance, usually dependent on the regulatory authority. It is legally recognized in the country as having the clinical and scientific knowledge required to compile, collect, analyze, and report drug safety data. It harmonizes the tasks of the local centers, manages the national database, and represents the country at international forums.

Counterfeit drug A counterfeit drug is a product in which the identity or source has been deliberately or fraudulently labeled incorrectly. Counterfeiting can apply to brand-name products and generic products, and counterfeit products may include products with incorrect ingredients, without active ingredients, with insufficient active ingredients, or with counterfeit packaging.³⁴

Cross-sectional study An epidemiological strategy in which observations about several 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, of 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

³⁴ Normas Jurídicas de Nicaragua. En línea <<http://www.bvspublica.org.ni/doc/farmacia/01.pdf>> [acceso septiembre de 2008].

population subgroups defined based on 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 whether onset of the disease studied or each of the variables considered occurred first.³¹

Data sheet A standardized form where essential scientific information about the proprietary drug considered is collected for distribution to health care professionals by the marketing authorization holder. It must be approved by the competent health authorities that have issued the marketing authorization.³⁰

Descriptive study A study that is designed solely for the purpose of describing the distribution of certain variables, but does not consider the associations between them. The study design is usually cross-sectional.³¹

Dosage form The physical form of the finished pharmaceutical product (e.g., tablets, capsules, syrups, suppositories). With the development of biopharmacy and specifically with recognition of the importance of bioavailability, dosage forms have acquired a more relevant role as systems of release or delivery of drugs or active ingredients. This concept has led to acceptance of the need to evaluate their fitness for release of the active ingredient, which is their primary characteristic.³⁶

Drug substance Any substance administered to humans for prophylaxis, diagnosis, or treatment of a disease or in order to modify one or more physiological functions.³⁶

Drug product 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 for medicinal purposes, or combinations of such substances that can be administered to persons or animals for any of these reasons, even if they are offered without explicit reference to such properties.³¹

Drug interaction Any interaction between one or more drugs, a drug and a food, or a drug and a laboratory test. The first two categories of interactions are important because of the effect they have on the pharmacological activity of the drug by increasing or decreasing desirable or adverse effects. The importance of the third category of interaction is related to the change that a certain drug can cause in the laboratory test results that influence their reliability.³³

Drug-related problems Health problems (i.e., negative clinical results) resulting from pharmacotherapy. Such problems occur for several reasons and lead to failure to achieve the therapeutic objective or onset of undesirable effects.³⁵

³⁵ Lacasa C, Humet C, Cot R. Errores de medicación. Prevención, diagnóstico y tratamiento. SEFH 1ª Ed EASO Barcelona 2001.

Drug withdrawal In assessment of the causal relationship, the event improves after the drug is withdrawn, regardless of the treatment received, and/or the drug was only administered once.³⁰

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.³¹

Efficacy Degree to which a certain intervention leads to a beneficial result in certain conditions, measured in the context of a controlled clinical trial. Demonstration that a drug is capable of changing certain biological variables is not proof of clinical efficacy (e.g., although some drugs can cause reduced blood pressure, this effect does not necessarily entail that they will be effective for reducing the cardiovascular risk of a hypertensive patient).³¹

Efficiency Effects or results obtained with a certain treatment related to the effort used to administer the treatment in terms of human resources, materials, and time.³¹

Essential drugs A group of drugs that are the basic, most important, and essential drugs required to meet the health care needs of most of the population. This concept was proposed by WHO in order to optimize the limited financial resources of a health system.³⁹

Excipient A substance lacking predictable pharmacological activity that is added to a drug in order 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.³⁶

Facsimile drug A drug marketed by a pharmaceutical laboratory that has not been granted marketing authorization. This can only occur when there is no current legislation on intellectual property rights (patents). Basically the legal protection of patents for drugs can refer to products or procedures; if they are for procedures, a laboratory can manufacture any drug that is protected by a procedural patent, as long as the method of acquisition is significantly different from that described by the inventor and the original manufacturer. Facsimile drugs are referred to by an alternative brand name.³¹

Fixed dose combination A pharmaceutical product that contains certain quantities of two or more active ingredients.³¹

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

Generic (see “generic drug”)¹²

Generic drug A drug that is distributed or dispensed labeled with the generic name of the active ingredient (i.e., without identification of the brand name or trade name).³¹

Good pharmacovigilance practices Set of standards or recommendations designed to guarantee: (1) authenticity of the data on drug-related risks collected for evaluation at all times; (2) confidentiality of the information related to the identity of the persons that have had or reported adverse reactions; (3) use of uniform criteria in evaluation of the reports and production of signs and alerts.³⁰

Harmonization Process of seeking consensus on drug registration requirements and procedures, and other regulatory affairs. Regulatory authorities and the pharmaceutical industry participate in this process.³⁶

Homeopathic drug A drug used in homeopathic medicine. The dosage form of such drugs may be solid or liquid, and they have very low concentrations of the active ingredient. In the homeopathic system, concentrations are expressed in a decimal system of attenuations or dilutions.

Hypersensitivity (see “allergic drug reaction”)¹²

iatrogenesis Abnormal or altered state due to the activity of the physician or other authorized personnel. In some countries, the term has a legal connotation since it refers to a situation caused by “improper or erroneous treatment”.³⁶

Imputability (see also “causality”) This is the case-by-case analysis of the causal relationship between drug administration and onset of an adverse reaction. It is an individual analysis used for reporting since it does not seek to study the potential risk of the drug overall or the importance of the risk associated with the drug in the population. Imputability methods are used to harmonize and standardize the imputation process, and to allow reproducibility by different evaluators.³⁰

Incidence A term that designates different measures to quantify the dynamic of an event in a group of subjects over a certain period of time.³⁶

Indication The use(s) that a product (e.g., drug, medical device, dietary supplement) is assigned after it has been scientifically demonstrated that its use for a given purpose is effective and safe. In other words, there is a rationale for such use in terms of the risk-benefit relationship provided by the product for prevention, diagnosis, treatment, relief, or cure of a disease or condition. The indications are included in the product labeling when they have been approved by the health authorities.³⁶

Indicator A variable that reflects the health status of a community and can be measured directly.³⁶

³⁶ WHO Collaborating Centre for Drugs Statistics Methodology. The ATC/DDD system. On-line: < <http://www.whocc.no/atcddd/>> [accessed September 2008].

Innovator drug This is usually the drug that was authorized first for marketing based on the quality, safety, and efficacy documents.³⁹

Intensity or severity of adverse reaction (see also “seriousness”) This is the magnitude of the effect in an individual induced by an adverse reaction, which can be described as mild, moderate, or serious depending on whether or not and to what extent it affects development of the patient’s daily activity. It is different from “seriousness”, which assesses the risk to the life of the patient associated with the reaction.³⁰

Intensive pharmacovigilance Pharmacovigilance method that consists of **systematically** obtaining **complete** and **quality** information on suspected adverse drug reactions characterized by high *sensitivity* and *reliability*, particularly when the frequency of adverse reactions, identification of predisposing factors, patterns of drug use, or other items must be determined.³⁰

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Organization founded in 1990 that holds periodic conferences with the participation of regulatory authorities and pharmaceutical associations from the European Union, Japan, and the United States and, as observers, other countries and WHO. The purpose of this organization is to prevent duplication of preclinical and clinical trials occurring due to different regulations in different countries and, in general, to standardize the regulatory processes for drugs and monitor their pharmaceutical quality.³⁷

International nonproprietary name for pharmaceutical substances (INN) Name recommended by WHO for each drug. Its purpose is to achieve identification of all drugs on the international level.³¹

Lack of efficacy (therapeutic failure, therapeutic ineffectiveness) Unexpected failure of a drug with regard to producing the expected effect as determined previously by scientific research.³⁶

Local pharmacovigilance center This is the functional unit linked to the health system that is responsible for conducting official pharmacovigilance programs in a specific area: planning, coordination, collection, evaluation, coding, training, and information on adverse drug reactions.

Medical device An article, instrument, apparatus, or artifact, including its components, parts, or accessories, that is manufactured, sold, or recommended for use in: (1) diagnosis, curative or palliative treatment or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans; (2)

³⁷ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). On-line: <<http://www.ich.org>> [accessed September 2008].

restoration, correction, or modification of a physiological function or body structure in humans; (3) diagnosis of pregnancy in humans; (4) care of humans during pregnancy or childbirth, or after birth, including care for the newborn. Medical devices do not achieve the purpose for which they are used through chemical action in or on the body; moreover, they do not undergo biotransformation during use.³⁶

Medical device vigilance Set of methods and observations that can be used to detect adverse incidents during use of a medical device that may cause harm to the patient, operator, or the surrounding environment. The problems, malfunction, harm, or potential harm from use of medical devices can be included in the term **adverse incident (AI)**.³⁸

Medication error or medical error An event that is avoidable, is caused by improper use of a drug that can cause injury to a patient, and occurs while the drug is managed by health care personnel, patients, or the consumer.³⁵

Meta-analysis A statistical method used widely in modern scientific research and increasingly in clinical pharmacology. It can integrate the individual results obtained in two studies, or usually in several studies, on a single subject. It is used to increase the total statistical power by combining the results of independent or previous research.³⁶

Monitoring Systematic data collection on the use of drugs. It should not be used as a synonym of drug surveillance or pharmacovigilance.³¹

Multisource drug 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 they are not protected by patents or because the patent holder has granted the license to produce or market the drug to other suppliers.³⁹

Notifier Any health professional that has suspected a probable adverse drug reaction and reported it to a pharmacovigilance center.³⁰

Observational study An analytical epidemiological study in which the researcher does not decide on assignment of subjects to each group, but rather merely records (observes) what occurs in reality. This term can be used for cohort studies, case-control studies, or cross-sectional studies.³¹

³⁶ANMAT, Administración Nacional de Medicamentos, alimentos y Tecnología Médica. Tecnovigilancia. En línea: < www.anmat.gov.ar/tecmed/tvg.htm > [acceso septiembre de 2008].

³⁹ WHO Expert Committee on specifications for pharmaceutical preparations. 40th Report. WHO Technical Report Series No. 937. Annex 7. Multisource (Generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability. Geneva, Switzerland. 2006.

Off-label use In the United States and some other countries, this refers to any use of a medicinal product that has not been 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 considered to be reasonable and modern, and on knowledge of the drug, the relevant literature, and the current prescribing practices and use by physicians.³⁶

Outcome Final course of an adverse drug reaction.³¹

Over-the-counter drug A drug with delivery or administration that does not require medical authorization. There may be different categories for these drugs in accordance with the legislation in each country. Therefore, the location for dispensing of these drugs may be limited to pharmacies or may occur in general commercial establishments. Dispensing or sale without prescription should not be confused with certification of unrestricted sale.⁴⁰

Package insert Information about the properties, indications, and precautions for use of a certain drug that occur and are included on the primary drug container.

Pharmacoepidemiology Study of the use and effects of drugs in large populations; drug epidemiology. Study of the consumption and effects of drugs or medication in the community, including drug use studies, clinical trials, and pharmacovigilance.³⁶

Pharmacogenetics Study of any change in pharmacological response due to hereditary causes.³¹

Pharmacovigilance Science and activities related to detection, evaluation, understanding, and prevention of adverse effects of drugs or any other drug-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. It has been suggested that, strictly speaking, a distinction should be made between monitoring and pharmacovigilance.^{36iv}

Set of methods used for identification, quantitative risk assessment, and qualitative clinical assessment of the effects of acute or chronic use of drugs on the total population or specific population subgroups.³¹

Pharmacovigilance database Computer system that can be used to record reports of suspected adverse reactions, after they have been evaluated and coded, and produce alerts or signs.³⁰

⁴⁰ Promoción de la salud. Glosario. OMS. Ginebra, Suiza. 1998. En línea. < http://www.bvs.org.ar/pdf/glosario_sp.pdf > [acceso septiembre de 2008].

Placebo Inert substance such as lactose that is used as a supposed drug. The suggestive effects associated with administration do not have pharmacological activity. In other words, a substance with pharmacological activity (e.g., a vitamin) used for a therapeutic purpose unrelated to its known pharmacological effects.³³

Placebo effect A result of use or administration of a placebo, which may be beneficial or adverse. The placebo effect is also part of the overall effect of an active drug and, consequently, of any medical treatment attributed to such drug.³¹

Predisposing factor Social, economic, or biological conditions, behavior, or environments that are associated with or cause increased susceptibility to a certain disease, poor health, or injuries.⁴⁰

Prevalence This usually refers to counting the cases of a disease or trait at a certain time in a given population. The phenomenon is quantified statistically, whereas incidence quantifies it dynamically.³¹

Proprietary drug A drug with a certain composition and information, 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.³⁰

Quality assurance All planned and systematic actions that are established in order to ensure that pharmacovigilance activities are conducted and documented in accordance with Good Pharmacovigilance Practices and the pertinent regulatory requirements.³⁰

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

Record linkage studies Studies conducted using the method of compiling information recorded in two or more registries (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.⁴¹

Re-exposure In assessment of the causal relationship, when the reaction or event occurs again after administration of the suspected drug.³⁰

⁴¹ D Capellà, JR Laporte. La notificación espontánea de reacciones adversas a medicamentos. En JR Laporte, G Tognoni - Principios de Epidemiología del Medicamento, 1993. En línea. <<http://www.icf.uab.es/pem/docs/cap8.pdf>> [acceso septiembre de 2008].

Reporting (see also “yellow card”) Communication of a suspected adverse drug reaction to a pharmacovigilance center. These reports are usually made by the adverse reaction reporting forms (yellow card), and seek to maintain data confidentiality at all times.³⁰

Reporting form (see “yellow card”)

Risk This is the probability that an event will cause harm, which is usually expressed as a percentage or rate.⁴¹

Risk-benefit relationship Relationship between the benefits and risks associated with use of a drug. It is used to express a judgment on the function of the drug in medical practice based on data about its efficacy and safety and considerations about factors such as possible improper use or the severity and prognosis of disease. The concept can be used for a single drug or for comparisons between two or more drugs used for the same indication.³¹

Risk factor A characteristic associated with onset of a disease that is congenital, hereditary, or due to exposure or lifestyle (*post hoc fallacy, ergo propter hoc*). A fallacy that involves arriving at a conclusion about causality based on observation of a clinical change in a patient that has undergone any type of therapeutic intervention. This fallacy has led to therapeutic use of many drugs with unproven efficacy prior to introduction of the controlled clinical trial. If the patient improved after administration of the drug, it was concluded that the drug was effective.³¹

Safety Characteristic of a drug that can be used with very low probability of causing unjustifiable toxic effects. Consequently, drug safety is a relative characteristic and it is difficult to measure in clinical pharmacology due to the lack of operative definitions and for ethical and legal reasons.³⁶

Serious adverse reaction Any reaction that is fatal, can be life-threatening, implies disability or invalidity, results in hospitalization or prolonged hospital stay, causes a persistent or significant disability or invalidity, or is a congenital abnormality or birth defect.³⁰

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 and/or justify discontinuation 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 ADR, the intensity and duration of the reaction as well as the general context in which it occurs should always be taken into account.¹²

Side effect (*efecto colateral*) (see “adverse drug reaction”) Any unintentional effect of a pharmaceutical product that occurs with normal doses used in humans, and is related to the pharmacological properties of the drug. 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.³²

Side effect (*efecto secundario*) An effect that does not occur as a result of the primary pharmacological action of a drug, but rather is an eventual consequence of such action (e.g., diarrhea associated with abnormalities in the normal bacterial flora balance induced by an antibiotic treatment). Strictly speaking, this term should not be used as a synonym of *efecto colateral*.³¹

Sign (see “alert”)

Source documents Original documents, data, and records such as hospital records, medical records, laboratory notes, memoranda, subject diaries, or evaluation checklists, pharmaceutical delivery records, data recorded from automatic instruments, copies, or certified transcriptions following verification that they are exact copies, microfiches, photographic negatives, magnetic media or microfilm, x-rays, subject files and records kept at the pharmacy, laboratories, and medical-technical departments involved in the clinical trial. All original documents related to pharmacovigilance reports, particularly: reports of telephone conversations or initial postal shipments by the notifier; internal notes by medical visitors; suspected adverse reaction reporting forms (filled out by the notifier or person in charge of pharmacovigilance; results of additional tests or hospital discharges; postal shipments (initial, follow-up, final); or computerized data lists (e.g., news, summaries, tables) related to reporting.³⁰

Spontaneous or voluntary reporting Information on adverse drug reactions obtained by voluntary reports of physicians, hospitals, and centers.³¹

Spontaneous reporting system A pharmacovigilance method based on communication, collection, and assessment of reports by health care professionals about suspected adverse drug reactions, drug dependency, drug abuse and misuse.³⁰

Statistical significance Probability that a difference observed will result from causality and not from the causal determinants of a study. If statistical significance is found, this does not necessarily imply clinical significance.³¹

Teratogenicity Capacity of the drug to cause harm to the embryo or fetus and, strictly speaking, structural defects occurring during any stage of development.³¹

Therapeutic ineffectiveness A drug-related problem that can occur in several different situations and is associated with inappropriate use, pharmacokinetic and pharmacodynamic interactions, or genetic polymorphisms.³⁰

Time sequence In assessment of the causal relationship, the time between introduction of treatment and onset of the first signs of the reaction is considered.³¹

Toxicity Degree to which a substance is harmful. Harmful phenomena caused by a substance or drug that are observed after administration.³⁶

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

Type B effects 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. In some cases they are immunological and they occur only in patients with predisposing factors, which are often unknown. Immunological reactions may range from rashes, anaphylaxis, vasculitis, or inflammatory organ lesions to highly specific autoimmune syndromes. Non-immunological Type B effects also occur in a minority of predisposed patients that are intolerant (e.g., due to a metabolic birth defects or acquired deficiency of a certain enzyme that results in an abnormal metabolic pathway or accumulation of a toxic metabolite).¹²

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

Type D effects These include carcinogenesis and teratogenesis.¹²

Unacceptable indication Any drug indication that is considered to be inappropriate, obsolete, or has not been recommended by the responsible authorities or well-known publications.³⁶

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.³¹

Undesirable effect This is a synonym of adverse reaction and adverse effect.³¹

Unexpected adverse reaction A reaction that has not been described in the product labeling or has not been reported to the health authorities by the laboratory that obtained the product registration when it was requested (see also “adverse drug reaction”). An adverse reaction of a nature or intensity that does not agree with the local information or marketing authorization, or cannot be expected based on the pharmacological characteristics of the drug. The predominant element in this case is that the phenomenon is unknown.³⁰

Uppsala Monitoring Centre (UMC) The Uppsala International Centre for Drug Monitoring dependent on WHO.³⁹

Validated reporting A report is said to be validated when the identity of the notifier and/or the origin of the report has been confirmed.³⁰

Verification Procedures required in pharmacovigilance in order to ensure that the data included in the final report reflects the original observations. These procedures can be used for the medical record, individual form data, lists, tables, and statistical analysis.³⁰

Vigimed This is the name of the e-mail distribution list maintained by the Uppsala International Centre for Drug Monitoring dependent on WHO. It allows pharmacovigilance centers around the world to rapidly exchange information about drug-related problems.³⁹

WHO Adverse Reaction Terminology (WHO-ART) A dictionary of terminology for adverse drug reactions that uses a coding system.^{42,43}

Withdrawal syndrome Onset of a predictable series of signs and symptoms resulting from abnormal activity, primarily of the central nervous system, due to sudden interruption or rapid reduction of drug administration.³⁶

Yellow card This is the yellow (white, light blue) form used to record suspected adverse reactions. It is distributed to health care professionals by the national pharmacovigilance program and used for reporting. It collects information about the patient (e.g., identification, age, sex, weight), the suspected drug (e.g., name, dose, frequency, date of onset and resolution, therapeutic indication), the adverse reaction (e.g., description, date of onset and resolution, outcome, effect of re-exposure if any), and the reporting professional (e.g., name, address, phone, position, health care level).³⁰

⁴² Seguridad de los Medicamentos, Nota descriptiva N°293. OMS 2005. En línea: <<http://www.who.int/mediacentre/factsheets/fs293/es/>> [acceso septiembre de 2008].

⁴³Adverse Reaction Terminology WHO-ART. On-line: < <http://www.umc-products.com/graphics/3149.pdf>> [accessed September 2008].

9. Abbreviations and acronyms

AERS: Adverse Event Reporting System, FDA

ANMAT: Argentine National Administration of Drugs, Food, and Medical Technology

ANVISA: Brazilian National Health Surveillance Agency

INN: International nonproprietary name

EMA: 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

PV: Pharmacovigilance

INVIMA: Colombian National Institute of Food and Drug Surveillance

ADR: Adverse drug reactions

WHO: World Health Organization

PAHO: Pan American Health Organization

UMC: Uppsala Monitoring Center

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

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

10. ANNEX I. Spontaneous Reporting Card Form

Patient data: (in order to avoid duplication of reports, at least the initials are required)

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

Patient data will be handled confidentially at all times

Brief description of adverse event	
------------------------------------	--

Brief description of patient's clinical symptoms	
--	--

Relevant additional examinations (with dates)	
---	--

Relevant medical conditions	
-----------------------------	--

Drug(s) (indicate the suspected agent first)

Generic name	Brand name	Daily dose	Route	Start (date)	Finish (date)	Therapeutic purpose	Number of doses received

Outcome:

Recovery	<input type="checkbox"/>	Did discontinuation or reduction of the dose of the suspected drug cause, reduce, or eliminate the adverse event?	Yes	No
Recovery with sequelae	<input type="checkbox"/>	Did re-exposure to the drug cause the same or a similar adverse reaction?		
Not recovered	<input type="checkbox"/>	Date of onset of event:		
Unknown	<input type="checkbox"/>			
Required or prolonged hospitalization	<input type="checkbox"/>	Report date:		
Defect	<input type="checkbox"/>			
Life-threatening	<input type="checkbox"/>			
Fatal (date)	<input type="checkbox"/>			

This data is confidential (it will be used only to communicate with notifiers)

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

Instructions for filling out the pharmacovigilance card:

Patient name: only initials can be indicated.

Weight: in kilograms. Use two decimals in children.

Height: in meters, with two decimals. This data is important when the patients are minors or cancer drugs are used.

Age: in years. If the patients are children under 2 years, the age should be stated in months and the date of birth should be added. When it involves birth defects, report the age and sex of the infant when it was detected. Add the mother's age.

Sex: use "F" for females and "M" for males.

Description of clinical symptoms: indicate the underlying disease and any previous medical condition of importance

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

If it involves birth defects, specify when the impact occurred during pregnancy.

In the event of lack of therapeutic response to a drug, it should be reported as an adverse event.

In cases of therapeutic failure, it is important to include more data on the drug (e.g., brand name, batch number, expiration date)

Drug or medicinal product: indicate the suspected drug, its generic name (INN), and brand name in the first place.

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

* Vaccines, advertising drugs, radioactive drugs, medicinal plants, magisterial formulas, homeopathic drugs, and medicinal gases must be considered drugs.

Indicate the daily dose. 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 medication.

CONSIDERATIONS ON THE REACTION

Result: After the reaction occurred, what was the final result? Mark the different situations with an "X"

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

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

Data on the reporting professional: This can be only initials and the essential data required to obtain a response or ask any questions if required.

11. ANNEX II Naranjo et.al. algorithm⁴⁴

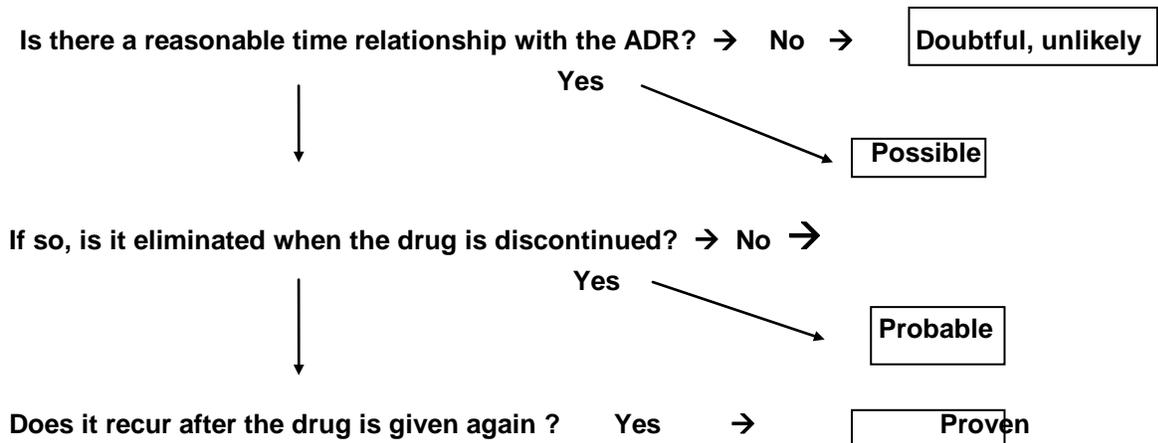
	YES	NO	Unknown	Points
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse reaction occur after the suspected drug was given?	+2	-1	0	
3. Did the adverse reaction improve after administration of the drug was discontinued or a specific antagonist was given?	+1	0	0	
4. Did the adverse reaction occur again after the drug was given again?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could have caused the reaction?	-1	+2	0	
6. Did the adverse reaction occur again after the placebo was given?	-1	+1	0	
7. Were toxic concentrations of the drug detected in the blood (or other fluids)?	+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 caused by the same drug or another similar drug in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORING				

Scoring:

Definite ADR: ≥ 9 points. Probable ADR: 5-8 points Possible ADR : 1-4 points Doubtful ADR: ≤ 0

⁴⁴ Naranjo et al, Clin Pharmacol Ther 1981. 30:239-45.

11. ANNEX II FDA Causality Algorithm



12. ANNEX III SUMMARY OF PHARMACOVIGILANCE RESPONSIBILITIES

<i>Patients, public</i>	Comply with the prescribed treatment and report adverse events to health representatives.
<i>Health care professionals</i>	Diagnose the adverse events. Manage the adverse events. Refer patients with serious and severe adverse events to the main hospitals for management and research. Perform a basic causality assessment. Report any suspected serious or unexpected drug-related adverse reactions or problems. Send such information as soon as possible to the appropriate local or national center by using the yellow card. Keep clinical documentation of adverse drug reactions Cooperate with the technical supervisors from the national pharmacovigilance system. Stay informed about safety data related to drugs that are usually prescribed, dispensed, or administered. Patient education. Prevent errors. Promote rational drug use. Follow the treatment guides. Communicate with patients and the public. Attend meetings in order to receive information from the appropriate pharmacovigilance center. Take action as indicated by the local pharmacovigilance center
<i>Hospitals and other inpatient centers</i>	Distribute the reporting forms to all hospital health care professionals. Receive, evaluate, and process the suspected adverse reaction reports sent by hospital professionals. Complete the required information that is not available with the notifier. Define the valid reports and send them to the coordinating center. Send information about fatal or serious cases occurring in the hospital to the coordinating center within 24 hours. Maintain confidentiality of patient and notifier personal data. Review and purify the reports received to prevent duplication. Study and review the available scientific literature in depth. Propose and develop pharmacoepidemiological studies in your hospital in order to evaluate the drug safety profile Respond to requests for information related to adverse reactions by hospital professionals. Promote and participate in training of health professionals and technical staff with regard to hospital pharmacovigilance and pharmacoepidemiology. Respect the standards and procedures established by the national health authorities. Provide feedback for the notifiers.
<i>Local pharmacovigilance</i>	Lead the pharmacovigilance team in your region.

centers

Implement, develop, and strengthen the territorial scope of reports.
Receive, evaluate, and process the reports on the territorial level
Reports of suspected serious adverse reactions should be sent to the coordinating center for the national pharmacovigilance system within 10 calendar days.
Publish and distribute reporting cards.
Document and validate report data, verify authenticity and agreement with the originals.
Maintain the reliability of the data reported.
Maintain the confidentiality of the personal data for the patient and the notifier.
Provide a timely and appropriate response to reports by professionals in order to encourage participation.
Filing and safekeeping of all reports.
Develop methods to obtain early signs or alerts.
Contribute to scientific progress.
Respond to requests for information by health care professionals and authorities.
Promote and participate in training for health care professionals.
Participate in national pharmacovigilance system meetings.
Establish a quality assurance system that ensures good pharmacovigilance practices.
Coordinate and complete investigation of adverse events.
Report the adverse events and follow-up details to the coordinating center and the appropriate person from the national pharmacovigilance system.
Evaluate the causal relationship
Make drug decisions on the local level.
Make decisions as advised by the safety expert committee.
Train and supervise the local health teams and centers.

National pharmacovigilance center

Act as reference center for pharmacovigilance.
Receive, evaluate, code, and enter the reports sent by the pharmaceutical laboratories in the database.
Monitor data safety and confidentiality as well as data integrity during transfer processes.
Coordinate the activities of peripheral centers.
Verify that all reports of suspected serious adverse reactions occurring in the national territory are recorded and reported as soon as possible.
Manage the national pharmacovigilance system database.
Ensure the quality of the database.
Develop methods to obtain early signs and alerts.
Coordinate follow-up of publication of adverse reactions.
Ensure that the data from the reports collected complies with good pharmacovigilance practices.
Establish contacts with national pharmacovigilance centers in neighboring countries.
Act as national reference center for the WHO international pharmacovigilance system
Inform the therapeutic committees and all competent agencies of urgent measures related to safety problems
Conduct studies designed to evaluate drug safety
Promote information and training on pharmacovigilance in all national health centers.
Return the reporting results to the notifiers (health care professionals) since they are the pillars of the system

<i>Expert Committee</i>	<p>Evaluate the risk-benefit relationship of drugs and issue recommendations when required.</p> <p>Propose studies and research related to pharmacovigilance</p> <p>Collaborate in coordination, planning, and development of the pharmacovigilance system in evaluation of post-authorization studies.</p> <p>Provide technical assistance.</p>
<i>Pharmaceutical laboratory</i>	<p>Report all suspected serious adverse reactions received from health care professionals</p> <p>Keep a detailed record of all suspected adverse reactions</p> <p>Designate and ensure the availability of a qualified professional that is responsible for pharmacovigilance tasks.</p> <p>Propose changes to the data sheet, labeling, and package insert</p> <p>Ensure there is a filing system that can be used to store the documents</p> <p>Establish an auditing program</p>
<i>National Regulatory Authority</i>	<p>Develop national policies and action plans.</p> <p>Create a national pharmacovigilance system.</p> <p>Designate and/or create an official coordinating center.</p> <p>Report and manage suspected adverse reactions.</p> <p>Prepare and/or review periodic safety reports.</p> <p>Continuous assessment of the risk-benefit relationship during the post-authorization period.</p> <p>Establish criteria to identify and assess the severity of signs or alerts.</p> <p>Supervise post-authorization safety studies.</p> <p>Periodic review of the scientific literature on spontaneous adverse reactions for authorized drugs.</p> <p>Cooperate with pharmacovigilance centers in drug safety studies.</p> <p>Verify that the pharmaceutical laboratories have drug monitoring programs</p> <p>Verify the pharmacovigilance activities conducted by pharmaceutical laboratories.</p> <p>Inspect compliance with good pharmacovigilance practices by pharmaceutical laboratories.</p>

Uppsala Monitoring Centre
 Technical Committee
 National Regulatory Agency
 Local pharmacovigilance centers
 Central pharmacovigilance center
 Pharmacists and other health professionals
 Physicians
 Pharmaceutical laboratories