Agência Nacional de Vigilância Sanitária

Regulatory Guide - Anvisa

Pharmacovigilance Plan and Risk Minimization Plan PVP/RMP

In accordance with RESOLUTION – RDC no. 4, dated 10/Feb/09 (DOU 11/Feb/09): Provides for pharmacovigilance norms for the holders of marketing authorization for medical drugs for human use.

Brasília, August 2009.

Regulatory Guide - Anvisa
Pharmacovigilance Plan and Risk Minimization Plan / PVP and RMP

This guide is divided into two parts:

Part I: General Aspects

Part II: Structure for the elaboration of the Pharmacovigilance Plan and the Risk Minimization Plan.

The following references were used as background documents for its development: ICH E2E, Vol. 9 A EMEA, Risk MAP – FDA.

PART I: GENERAL ASPECTS

A risk management system may be defined as a a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those interventions

The Pharmacovigilance Plan (PVP) and the Risk Minimization Plan (RMP) with the correspondent safety specifications compose the MAH risk management system. Those are risk management documents per drug and should be handed to the Regulatory Authorities. If necessary, these documents may be integrated, as provided for in Chapter 6 of RDC no. 04/2009.

The PVP application will be required in the following situations:

- For all new synthetic, semi-synthetic molecule entities, new vaccines and biotechnology-derived products;
- Significant changes to the market authorization (e.g., use extension), unless the Regulatory Authority deems unnecessary;
- When an unexpected damage is identified;
- When requested by the Regulatory Authority.

If the measures proposed in the PVP are not enough to address the identified, potential or unknown risks, the elaboration of a RMP is necessary to supplement the actions described in the PVP.

1. INTRODUCTION

The main focus of this guide is the preparation of the Pharmacovigilance Plan and the Risk Minimization Plan, providing safety specifications that can be presented particularly at the moment of authorization request, but they may be used at any moment in the post-marketing period.

A medicinal product risk management system development, implementation, and assessment are part of the pharmacovigilance effort to promote a satisfactory benefit-risk balance, within the specified use conditions of the product.

The knowledge related to a product's safety profile may be altered in time, due to the extension of its use in terms of patients' characteristics and due to the number of exposed patients.

The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

According to the Periodical Pharmacovigilance Report (PPR), the follow-up of plans will be carried out by section 1.4.7 of the PPR, meeting the deadlines established for the PPR. If there is a substantial change in PVP and RMP, a new version of the plans should be submitted.

This guide describes a method to summarize the identification of important risks of a new medicinal product, significant potential risks, and critical information previously unknown at the moment of marketing authorization, including the populations that will be potentially at risk, and situations where the product is susceptible to being used, which were not studied in the pre-approval period. A Pharmacovigilance Plan and Risk Minimization Plan structure is thus proposed.

1.1 Objective

This guide is considered a regulatory document, and aims at providing practical guidance on the preparation of PVP and RMP and the elaboration of the corresponding safety specifications by the marketing authorization holders (MAH), particularly for new medicinal products, in accordance with RDC no. 04 of 10 February 2009 (DOU 11/Feb/2009).

1.2 Legal framework

Article 11 of RDC 04/2009 provides for the possibility of request by Anvisa, at the moment of authorization or at any moment, of the Pharmacovigilance Plan from pharmaceutical companies, with the description of routine actions or additional actions proposed for the surveillance of medicinal products. In additional, Article 12 describes that a Risk Minimization Plano may also be required for any product, in the case of safety situations that need additional actions.

1.3 On the development of the Plans

1.3.1 Safety Specifications

The PVP and the RMP should present an initial section denominated Safety Specifications, which is a summary of the known safety profile of the product and includes exposure data from clinical studies and from post-marketing use. Any safety considerations are discussed in this section, once they are a potential risk, as well as other aspects related to the product use, such as misuse, abuse, and off label use. An important consideration on safety specifications is the epidemiology section, which should present information on the population that would probably be exposed to the product (target population) and the relevant co-morbidities of this population.

1.3.2 Pharmacovigilance Plan

In general, the Pharmacovigilance Plan is specifically elaborated for a product and describes in detail the pharmacovigilance measures related to the potential risks and the ones identified in the safety specification. This plan should describe in detail the routine pharmacovigilance activities (e.g. sign detection) carried out by the MAH for the specified product.

The PVP should register, for each identified or potential risk, a specific measure to be used to monitor the risk, as well as gather future information, in addition to the studies planned, aiming at increasing the product safety knowledge. Such measures may include routine pharmacovigilance activities, as well as clinical, pharmacoepidemiological, and even pre-clinical studies, when applicable.

For products for which no special concerns have arisen, routine pharmacovigilance (see annex 1) should be sufficient for post-approval safety monitoring, without the need for additional actions (e.g., safety studies), then only a Pharmacovigilance Plan is necessary. However, for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered in a Risk Minimization Plan.

The section on RMP should provide a description of the necessary measures to minimize each identified or potential risk mentioned in the safety specifications. Specific risk minimization measures are not necessarily compulsory for a product. However, if such measures are not expected or considered, a justification should be given to ensure that the measures mentioned in the PVP are enough to address any identified or potential risk previously risen.

1.3.3 Risk Minimization Plan

The RMP aims at managing new risks identified in the post-approval period or even the follow-up of risks known in previously studied populations. It also aims at being applied to situations where the product will have a probable use that was not adequately studied in the pre-approval period.

In addition to the pharmacovigilance routine, the RMP should present a proposal based on pharmacoepidemiological methods when there is the need to assess critical points related to the medicinal product safety. Other methods may be used in the RMP, such as: informative and educational material; use restriction (hospital x ambulatory); dispensation control (prescription retention); informed consent requirement; restricted access and patient record programs. The MAH should justify the method proposed for the execution of its RMP. In this plan, the company should explain how it will assess the effectiveness of its actions to minimize the risk posed by their products.

PART II: MODEL STRUCTURE FOR THE ELABORATION OF THE PHARMACOVIGILANCE AND RISK MINIMIZATION PLANS

The detailed instructions for the elaboration of a PVP/RMP by the MAHs are described below.

The model serves as guidance to help the filling-up of the PVP/RMP, and is only a filing-up guidance. It should not be written identically.

The system adopted was the following:

1) Information in *Double-underlined italic*: data that should be replaced according to the filling up of each Plan.

Example: On the cover, the data related to "*First and last names, initials*" should be replaced with the company's data.

2) Information in Italic: instructions or guidance for filling up the field.

Example: On the cover, the field "*Name of product: active substance*" has the following guidance: "*do not use trade name, use generic name only"*

Cover

The cover will be the first page of the Plan and aims at providing the information to identity the company, the Pharmacovigilance area, the product, and the period mentioned in the document.

The following information should be included on the cover of the document:

1.1. Name of product: trade name and active substance

1.2. Name and address of Company: corporate headquarters or other company responsible for elaborating the Plan

1.3. Local Pharmacovigilance contact:
- Name of the person responsible for the Pharmacovigilance area (according to RDC 04/2009 Art. 3)
- Job
- Department

- Address
- Telephone
- E-mail

1.4. Database lock point.

1.5. Date of document: *date of document elaboration conclusion*.

1.6. Number of document: *sequence order*.

1.7. Declaration of confidentiality: *text informing that the document is confidential to regulatory authorities and MAHs, and its use and reproduction is not allowed for other purposes*.

Cover Example:

Name of product: active substance
- do not use trade name, use generic name only

PHARMACOVIGILANCE PLAN

AND

RISK MINIMIZATION PLAN

Author(s):	*First and last names, initials*
Type of document:	*Risk Management Plan*
Database lock point:	*dd/mmm/yyyy*
No. of document	*XXX*
Date of document:	*dd/mmm/yyyy*

Declaration of Confidentiality

Table of Contents

A) Pharmacovigilance Plan (PVP)

1. Safety Specification

Post-approval safety issues are essential concerns of the industry responsible for the development of new medicinal products. Since the initial period of clinical trials, the company should have concerns on these issues. At the end of this period, the company will have an overview of the drug safety, elaborating a background document denominated Safety Specification. The Pharmacovigilance Plan is derived from the knowledge obtained during the pre-approval development period, and concretized by means of the Safety Specification.

The Safety Specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period. This Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan. The Safety Specification can be built initially during the pre-marketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed during development.

1.1 Non-clinical data

This section should present non-clinical safety findings that have not been adequately addressed by clinical data, or that have unknown significance, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.);
- Drug interactions;
- Other toxicity-related information or data.

If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

Example:

General safety pharmacology: cardiovascular (including QT interval prolongation), nervous system, polymorphic metabolism, etc.

Mechanisms for drug interaction

Other toxicity-related information or data

Table 1.1 Safety Problems with Inadequate/ Unknown Information

Safety problem (from non-clinical studies)	**Relevance for human use**
Repeat-dose toxicity	
Reproductive toxicity	*A summary of the important findings should be included (also negative results) if the drug is to be used in potentially reproductive women.*
Developmental toxicity	
Etc.	

Source: XX

Specify the need of non-clinical data, if the product is to be used in special populations (e.g. the elderly, pregnant women, and children).

1.2 Clinical Data

1.2.1 Limitations of the Human Safety Database

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

Example:

Example: Table 1.2.A Exposure Duration Clinical Study

Indication		
Exposure duration	**Individuals**	**Individuals-time**
At least 1 month		
At least 3 months		
Etc....		

Source: XX

Example: Table 1.2.B Dosage Exposure Clinical Study

Indication		
Exposure dosage	**Individuals**	**Individuals-time**
Dosage level 1		
Dosage level 2		
Etc....		

Source: XX

Example: Table 1.2.C Post-Marketing Exposure per Age Group and Gender

Indication				
Age group	**Individuals**		**Exposure (e.g. packages or individuals-time)**	
	Men	Women	Men	Women
Age group 1				
Age group 2				
Etc.				

Source: XX
Write the source of information on the SAFETY PLAN annex

1.2.2 Populations not Studied in the Pre-Approval Phase

The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Populations to be considered should include (but might not be limited to)

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Example: Table 1.2.2 Populations not Studied in the Pre-Approval Phase

Number of study	**Number of patients exposed to this product in**	**Age range**	**Exclusion criteria for the study**

	the study		
Study 1			
Study 2			
Etc.			

Source: XX

1.2.3 Post-approval Experience

Updates related to Safety Specification should be made in accordance with the real exposure standard, when compared to the recommendations in the Drug Safety Reference Document (DSRD). New safety concerns should be mentioned, particularly in previously not studied populations. The safety regulatory actions carried out should also be mentioned.

1.2.4 Adverse Events

This section should list the important identified and potential risks that require further characterization or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented.

Example: Table 1.2.4 Relevant Identified Risk: XX
(this should be elaborated for each relevant identified risk)

Item	Details
Identified risk	*Use MedDRA or Who-Art terms.*
Severity/ results	*If available, register the distribution (e.g., % of fatal cases, % of recovered with/ without treatment/sequels. % of non-recovered, % of hospitalized, etc.).*
Frequency with confidence intervals	*Provide relative and excessive frequency (placebo or comparative), as incidence rates and incidence risk for populations:* *1) only blind and random study population* *2) all clinical study populations (including open extension)* *3) epidemiological studies stratified per indication* *When there are evident differences in rates among populations, this should be discussed.*
Basic incidence/ prevalence	*Consult Epidemiology.*
Risk groups or factors	*Describe the data on use, dosage, time, and susceptibility, or other factors, when available. It is possible to provide a cumulative risk function (time curves until the event).*
Potential Mechanisms	
Avoidability	*Provide data on predictability or avoidability of the adverse event.*
Potential public health impact of the safety issue	*Describe or list, if possible, using, for instance, numbers required for the damage and/ or expected number of affected patients, hospitalizations, or fatalities in the*

	expected user population.
Regulatory action taken	*Include country and type of action. For example, was there a Health Authority request for this risk to be added on the label? Is there any black box warning related to this risk?*
Evidence source	*Identify and cross-reference with support data in the dossier, or annex data, or post-marketing clinical studies, safety studies, pharmacoepidemiological studies, PPR, other safety reports, etc.* *This should be provided per author.*

1.2.5 Identified and Potential Interactions, Including Food-Drug and Drug-Drug Interactions.

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

The following information should be provided for each interaction. Repeat the table as required for additional interactions.

Example: Table 1.2.5 Identified and Potential Interactions

Interacting substance	**Details**
Effect of interaction (including *MedDRA/ WhoArt* terms if appropriate)	*Provide the medical description of the interaction effect (e.g., peripheral neuropathy)*
Possible mechanism	
Potential health risk	
Discussion	

Source: XX

1.2.6 Epidemiology

The epidemiologic data of diseases covered by the drug indications should be presented. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, if this information is available.

Example: Table 1.2.6. Target-Population Epidemiology

Indication/ target population	
Incidence of target-indication	*Observe if a specific intercountry variation is known*
Prevalence of target-indication	

Mortality in target-indication	
Potential health risk	*Observe if a specific intercountry variation is known*
Discussion	*Provide age-sex distribution*

Source: XX

Example: Table 1.2.6.B Co-morbidity of Target-Population, per Indication

	Incidence	**Prevalence**	**Mortality**	**Main co-prescribed drugs**
Indication 1				
<Co-morbidity 1> in target-population				
<Co-morbidity 2> in target-population				
Etc...				

Source: XX

1.2.7 Pharmacological Class Effects

The Safety Specification should identify risks believed to be common to the pharmacological class.

Example: Table 1.2.7 Pharmacological Class Effects

Risk	**Frequency of drug adverse event in clinical studies**	**Frequency observed with other products in the same pharmacological class (source of data/ reference material)**	**Comment**
Risk 1		*Example:* *Product A, 35%* *Product B, 5%* *Product C, 0.5%* *Source: Vervloet D, Durham S, 1998*	
Etc...			

1.2.8 Additional Information

Other information related to potential safety issues may be included in the Safety Specification, such as:

- overdose;
- transmission by infectious agents;
- misuse;

- off-label use;

- unapproved use for pediatric population.

1.3 Summary

At the end of the Safety Specification a summary should be provided of the:
- Important identified risks;
- Important potential risks;
- Important missing information.

MAHs are encouraged to summarize specific ongoing safety issues on an issue-by-issue basis, including both non-clinical and clinical data that are pertinent to the problem.

Example: Table 1.3 Ongoing Safety Issues

Important identified risks	*List here*
Important potential risks	*List here*
Important missing information	*List here*

2. Topics of the Pharmacovigilance Plan

This section aims at guiding the elaboration of a pharmacovigilance plan.

2.1 Routine Pharmacovigilance Practices

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a Pharmacovigilance Plan. This routine pharmacovigilance should include the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- The preparation of reports for regulatory authorities:
    - Expedited adverse drug reaction (ADR) reports;
    - Periodic Pharmacovigilance Reports (PPRs).
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities;
- Other requirements, as defined by local regulations.

Example:

Use the text provided below as a suggestion and adapt it to your company's reality.

The following list presents examples of tools of "Name of Company" to carry out routine pharmacovigilance activities:

- *A validated global electronic database for permanent retention and recovery of all spontaneous reports (SRs) of adverse events and all serious adverse events (SAEs) of clinical studies phases 1-4 and post-marketing studies (e.g., records, safety studies).*
- *A validated data research tool and a validated hypothesis generator to identify potential safety signs based on pré-defined criteria and methodologies.*
- *A validated global electronic system to maintain and provide access to the pharmacovigilance Standard Operational Procedures.*
- *Etc...*

The following list presents examples of activities of "Name of Company" to carry out routine pharmacovigilance activities:

- *Daily review of individual cases of serious/ unlisted SRs and SAEs evaluated as serious/ listed/ related.*
- *Weekly review of listings for all the other SE/ SAE categories.*
- *Preparation of reports to health authorities, including Periodical Pharmacovigilance Reports, Annual Safety Reports, and the equivalent safety summaries required by individual health authorities.*

- *Close monitoring of important potential and identified risks in the PPR to additionally characterize the risk (analysis of frequency, severity, specificity, or risk factor detection).*
- *Continuous monitoring and safety profile management of investigational and marketed products, including sign detection, safety risk evaluation, labeling updating, evaluation of the need to take risk minimization measures, and communication with health authorities, as appropriate.*
- *Etc...*

2.2 Action Plan for Safety Issues

The Plan for each important safety issue should be presented and justified according to the following structure:

- Safety issue;
- Action(s) proposed;
- Objective of proposed action(s);
- Rationale for proposed action(s);
- Monitoring by the MAH for safety issue and proposed action(s);
- Milestones for evaluation and reporting.

Example: Table 2.2 Detailed Plan of Action for Safety Issues

Safety Issue 1	**Details**
Action(s) proposed	*Routine pharmacovigilance, including PPR cumulative analysis.* *List the additional actions proposed, using clear and accurate terminology. If you propose directed follow-up of determined cases, specify:* • *Post-marketing and/ or clinical study cases,* • *Only serious cases or all cases,* • *Only unlisted cases or all cases.* *Consider how you will implement these activities. Who will carry out which action and how will this be done?*
Objective of proposed action(s)	*Describe the objective of each action, e.g., directed follow-up designed to identify and/ or characterize the following:* • *Clinical characteristics of the events (laboratory abnormality standard, severity, results, new types of rare but serious events)* • *Types of patients at risk (demographic factors)* • *Risk factors (factors within the medical history)* • *Exposure characteristics (dosage, duration, co-medications)* *Show the text to be altered, if required: the routine pharmacovigilance aims at closely monitoring, evaluate, and additionally characterize the symptoms of this risk.*

Rationale for proposed action(s)	*Mention why the "Name of Company" believes the actions proposed are appropriate.*
Describe in details the additional measures that may be taken based on the results from this action and on the decision criteria to begin such measures	*Describe the possible consequences of the study results, if applicable* *Sample the text to be altered, if necessary:* *If there are new safety data, providing evidence of severity increase, specificity or risk frequency, to the regulatory authority, the Pharmacovigilance/ Risk Minimization Plan will be revised and updated. In addition, the DSRD section Adverse Reactions and the Investigator's Brochure will be updated and communicated.* *If new information leads to a change in the benefit-risk balance of this drug, the Health Authorities will be immediately notified.*
Milestones for evaluation and reporting to the Regulatory Authority, including rationale for milestone choice	*Mention when you will evaluate the effectiveness of activities and report the results to the Regulatory Authority. Justify chronogram choice.* *Sample the text to be altered, if necessary:* *PPRs are sent to the Health Authorities in accordance with the local periodicity requirements. For studies as declared in summary table 5-2.*
Code of study and titles of protocols (annex the complete study protocols and provide cross reference with its location in Annex 5)	*Write here*

2.3 Pharmacovigilance Plan Summary

At the end of this section, there should be a summary of the PVP presented.

In the table below, present a list of actions to be concluded (ongoing and planned) with milestones and chronograms.

Example: Table 2.3 Notable Actions and Milestones

Actions	**Milestones**	**Milestones / date**	***Status* of study**
Action 1			
Action 2			

2.4 Evaluation of the need to elaborate the Risk Minimization Plan

This section should have a discussion on the need of a RMP or not, in addition to the PVP, on safety concerns.

A review on potential or real problems, related to medication errors, overdose, pediatric use, off label use, transmission of infectious agents, misuse, among others, should be made.

B) Risk Minimization Plan (RMP)

After establishing the Pharmacovigilance Plan, the need or not of a Risk Minimization Plan should be assessed.

The Risk Minimization Plan (RMP) should be developed in addition to the Pharmacovigilance Plan, in safety situations where additional actions are needed. In this plan, the company should explain how it will assess the effectiveness of its actions to minimize their products' risks.

The RMP referred to in this article aims at managing new risks in the post-approval period, or even following up known risks in already studied populations. It also aims at being applied to situations where the product will have a probable use that was not adequately studied in the pre-approval period.

1. Risk Minimization Activities

The Risk Minimization Activities may comprise actions that aim at providing information on the product and actions related to the drug use control.

2. Effectiveness of Risk Minimization Activities

Methodologies to assess the effectiveness of the actions proposed should be developed for each risk minimization plan. The effectiveness indicators are related to the actions taken. Therefore, they will be specific for each plan.

3. Risk Minimization Plan for Safety Concerns

The risk minimization plan details the activities proposed to reduce the risks associated with individual safety concerns. When a plan is developed, the safety concerns discussed in the Safety Specification should be listed, and additional risk minimization measures should be proposed. In the case of each additional risk minimization activity proposed, the measurement of its effectiveness in risk reduction should also be described in detail.

The risk minimization activities should have defined objectives that result in specific processes or behaviors. An individual safety concern may have more than one risk minimization action linked to an objective.

Examples of actions:

- "Dear Doctor" letter;
- Patient recording and restrict distribution;
- A plan for a known teratogen could have the objective of avoiding any patient taking the drug becoming pregnant. A routine risk minimization activity might be to emphasize the need for effective contraception in the Summary of Product Characteristics and a recommendation that patients should have a negative pregnancy test before each prescription;
- Educational pack to provide information to the patients on the risks of the medicine;
- Limit the pack sizes to one month's supply of the medicine.

Example: Table 3 Risk Minimization Plan for Safety Problem

Item	**Details**
Routine risk minimization activities (i.e., product information, labeling and packaging)	*Provide a short description of what will be included in the DSRD, labeling, etc. to minimize risks (e.g., warning in the DSRD Section that "care should taken with patients with cardiac insufficiency, etc.")*
Additional risk minimization activity 1 (e.g., educational material or training programs for prescribers, pharmacists and patients, restricted access programs)	*Write here the name of the activity*
Objective of the activities proposed	*Write here*
Rationale for the activities proposed	*Write here*
Action proposed	*Write here*
Criteria to be used to verify the success of the minimization activities proposed (monitoring)	*Describe the plans to monitor periodically the activity effectiveness and identify activities with bad performance or ineffective activities as soon as possible after the implementation* *Write here*
Review period proposed	*Write here*
Etc...	*Write here the name of the activity*

III - REFERENCES

1. **EMEA** – Volume 9A of The Rules governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use, Set 2008.
2. **PHARMACOVIGILANCE PLANNING E2E**. INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. 2005, 29 p. (acessado em 17/05/2009 em http://www.ich.org/MediaServer.jser?@_ID=1195&@_MODE=GLB
3. **FDA's Guidance on Pharmacovigilance Parctices and Pharmacoepidemiological Assessment** – Risk Minimization Action Plan (Risk MAP) – FDA, May 2005.
4. **Current Challenges in Pharmacovigilance:** Pragmatic Approaches. Report of CIOMS Working Group V. 2001.
5. PHARMACOVIGILANCE, 2 ed. Editores **RONALD D. MANN e ELIZABETH B. ANDREWS.** John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, 2007. 688 p.
6. **Good Pharmacovigilance Practice Guide.** London: Pharmaceutical Press, 2009. 211 p.

APPENDIX

ANNEX 1 – Pharmacovigilance Methods

Passive Surveillance

Spontaneous Report

A spontaneous report is every suspected adverse drug reaction communicated by healthcare professionals to pharmaceutical companies or pharmacovigilance center.

The spontaneous report may provide risk information related to groups, factors and clinical issues related to the knowledge on serious adverse reactions. It can potentially cover the whole drug user population, all marketed drugs, ambulatory and hospital patients, and it is also possible to be assessed by the patient. It is considered a non-interventionist method as sign hypothesis generator and of low cost. It is the preferable method to begin a pharmacovigilance system, regardless the fact of being local, regional, national, or international.

However, there are limitations to the analysis of the data from spontaneous notifications, particularly when comparing the data among the several marketed drugs. One of the greatest limitations is underreporting followed by the difficulty to detect late reactions, unknown number of patients exposed, presentation of deviations, and the fact that causal relation hypotheses are not tested.

In addition, the spontaneous report method presents variable reporting rates over time due to factors such as reaction severity, drug marketing period, promotional appeals, development and promotion of the reporting system, and the publicity of a specific reaction.

Reports represent notification rates only, and not incidences of adverse reactions.

Despite the great limitations, spontaneous reporting is easy to be implemented, and is one of the most traditional pharmacovigilance methods.

Some techniques have been developed to assess data from spontaneous reports, such as case series.

Case Series

Series of case reports are useful for generating hypotheses and can also provide evidence of an association between a drug and an adverse event.

There are certain distinct adverse events known to be associated with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome (they may be denominated special interest reactions). Thus, when suspected adverse reaction reports are sent to a pharmacovigilance center, a survey of the cases already reported in the database should be carried out, as well as an assessment of the most common characteristics and the follow-up of the case outcome through monitoring. A case series should be carried out using, for instance, classification by key subsets, such as: origin (Institution/ State); drug use indication (CID 10); adverse reaction; manufacturer/ dosage forms; manufacture batches; dosages (low, medium, high); duration of treatment/ use of suspected drug; reaction occurrence period (epidemiological weeks or months); age range of the patients; other pertinent characteristics.

When carrying out case series, the following criteria should be considered: exclusion of duplicated reports (i.e. reports on a same reaction, with the same drug of a given patient, in a same period of time); if there is causality applied in all cases, exclusion of the reports where the reaction causality is not related to the drug; classify into key subsets, as described above; check the description in the literature regarding the drug-ADR relation occurrence frequency issues, existence of occurrence of only one trade, dosage, age range, or other specificities; check the need to collect more reports and consultation of manufacturers, observing if the drug-ADR relation was reported in the retrospective period of one year; check the possibility of variations along different periods.

Intensified reporting

This is the use of methods that stimulate and facilitate reporting by health professionals in specific situations. Some of these methods may include online reports in specific systems. Although these methods may cause an increase in the number of reports, they are not free from the limitations pertinent to the passive method of surveillance, particularly related to selection and verification.

Active Surveillance

Active surveillance seeks to ascertain more completely the number of adverse events in a given population via a continuous organized process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact.

In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. This method also allows carrying out surveillance not only through a medicinal product of interest but also by means of adverse reactions or population subgroups (i.e. pregnant women, newborn babies, the elderly, patients with kidney or liver insufficiency etc.), which may be part of a monitoring program.

Sentinel Sites

Active surveillance may be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with information collection, selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centers. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings may provide an efficient active surveillance system. Intensive monitoring by sentinel sites may also

be useful for the identification of risks in patients receiving orphan drugs, among other examples.

Prescription Event Monitoring

Prescription event monitoring is a method of active pharmacovigilance surveillance where patients are identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. Limitations of prescription event monitoring include incomplete physician response and the wide range of data collected, which may hide important signs. In addition, maintaining the patient's confidentiality may be a concern. The main advantage is the possibility of obtaining a great number of data from physicians and patients. The United Kingdom, New Zealand and Japan(27; 55) have been using this method to generate hypothesis, denominated PEM (Prescription Event Monitoring). PEM is also designed to supervise prescription occurrences.

Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of patient data of interest, may collect a battery of information using standardized questionnaires in a prospective fashion. This method is commonly denominated "Record-Linkage". These registries may be useful for conducting studies of case control and cohort types, and any other epidemiological method. They may help collecting data on the exposure to drugs and other factors associated to the clinical conditions of patients. This approach may be useful for amplifying a sign, particularly for rare outcomes. It is a fast method, often of low cost, but its weakness is the possibility of presenting incorrect data.

Comparative Observational Studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. The main types of observational studies are briefly described below.

Cross-sectional Study

"Cause" and "effect" detected simultaneously and data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecological analysis, where the observation unit is a set of individuals. The best application of cross-sectional studies occurs when the exposure is not altered over time.

Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure to the medicinal product among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio (OR), which is an estimate of the relative risk (RR) of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (pregnant women, newborn babies, the elderly, or any specific clinical conditions). For rare adverse events, existing large population-based databases may be useful and efficient. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify risk factors for a given adverse event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

Cohort Study

In a cohort study, a population-at-risk for a disease or event is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. Cohort studies are useful when there is a need to know the incidence rates of adverse events. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a given product or to study very rare outcomes. Similarly to case-control studies, the identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (pregnant women, newborn babies, the elderly).

Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing (pharmacogenetics) can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients (18) and normal volunteers.

These studies may be used to determine and quantify the level of risk or benefit in special subpopulations, which were not adequately assessed in the pre-approval clinical trial period. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. In addition, large trials are also resource-intensive. In drug regulatory agencies, this approach has brought the studies developed in the areas of pharmacovigilance and clinical research closer.

Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events or establish the prevalence of the use of drugs in specified populations.

Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence or prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns or adverse events. These studies examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses. One of the assessment measures is the calculation of the Attributable Risk to a given outcome, which seeks to identify if there is an additional risk rate among the exposed patients (an ADR of interest), compared to the non-exposed ones, thus using the determination of a background rate in the population for the given outcome.

Drug Utilization Study

Drug utilization studies describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations and to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. In general, the methods of Daily Dosage (DD) and Defined Daily Dosage (DDD) are used. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, in order to determine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

ANNEX 2 - GLOSSARY

Additional risk minimization activity: A not-routine risk minimization activity established to reduce the probability of an adverse reaction occurring or its severity should it occur. Examples are drug administration training or additional educational material.

Identified Risk: an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include:

- An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest suggests a causal relationship;
- An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Important Missing Information: information about the safety of a medicinal product, which is not available at the time of authorization request and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Potential Risk: an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples of potential risk include:

- Non-clinical safety concerns that have not been observed or resolved in clinical studies;
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship.
- A signal arising from a spontaneous adverse reaction reporting system.
- An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

Risk Management System: set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of such interventions.

Risk Minimization: set of activities used to reduce the probability of an adverse reaction occurring or its severity should it occur.

Routine Pharmacovigilance: Activities for all medicinal products of MAHs that are part of the Pharmacovigilance Plan. Additional actions for a particular product are not included here. Routine pharmacovigilance activities should include, among others:

- Systems and processes that ensure that information about all adverse reactions are collected and reported by the personnel of pharmaceutical companies;
- The regular preparation of Periodical Pharmacovigilance Reports and notification of adverse events to the health authorities;
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and updating of regulatory information;

Routine Risk Minimization Activities: Activities developed to warn and inform on an adverse event, aiming at reducing the probability of its occurrence. Different methods may be applied.

Safety Concern: An important identified risk, important potential risk, or important missing information that could impact on the risk-benefit balance of the product or have implications for public health.

Significant Change in Indication: When the target population differs from the previously authorized one. This includes, but is not limited to, a new disease area, a new age group (for example, pediatric indication).

Target population: The Patients who might be treated by the medicinal product according to the indication(s) and contraindication(s) in the Summary of Product Characteristics.

ANNEX 3 – ABBREVIATIONS

DSRD: Drug Safety Reference Document

MAH: Marketing Authorization Holder

PPR: Periodical Pharmacovigilance Report

PVP: Pharmacovigilance Plan

RMP: Risk Minimization Plan