



Regulatory Guide - Anvisa

Good Pharmacovigilance Practices and Inspection (GPPI) for MAHs

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.

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Guide – Good Pharmacovigilance Practices and Inspection (GPPI) for MAHs/ ANVISA

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1. INTRODUCTION

1.1 Objective

This guide is considered a regulatory document and aims at providing practical guidance for ensuring that the Pharmacovigilance Regulatory and Inspection obligations are met, as well as at preparing MAHs and the Brazilian Health Surveillance System (SNVS, in Portuguese) teams, as determined by RDC no. 4 of 10 February 2009 (DOU 11/Feb/2009).

This guide is based on documents *VOLUME 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – PART I: Guidelines for Marketing Authorisation Holders*, EMEA, September 2008, and the GOOD PHARMACOVIGILANCE PRACTICES FOR THE AMERICAS. Draft 9, November 2008. *Pan American Network on Drug regulatory Harmonization. Working Group on Pharmacovigilance*, adapted to the Brazilian reality, with a view to establish a harmonious relation with international criteria.

1.2 Legal framework

RDC 04/2009, in Chapter 7, from Article 13 to 16, provides for pharmacovigilance inspections. The MAH will be submitted to pharmacovigilance inspection by the SNVS whenever there is a need to assess the compliance to this Resolution. In addition, pharmacovigilance inspections will aim at assessing the pharmacovigilance systems of pharmaceutical companies, and may be carried out on a regular or sporadic basis.

The pharmacovigilance inspections will be based on documental analysis, interviews, institutional visits, database review, and verification of the compliance of legal requirements. Any documents related to the company's pharmacovigilance system and this Resolution may be required.

In addition to the pharmacovigilance inspections by the SNVS, the marketing authorization holders should carry out, at least once a year, a self-inspection related to the pharmacovigilance actions, keeping with them the self-inspection report with the description of the necessary corrective actions

The companies should have a registration document of the self-inspections carried out. The results from those self-inspections and their corrective actions should be part of an improvement process. The companies should have Standard Operational Procedures to carry out their self-inspections. The self-inspections should be recorded in documents to be kept for at least three years.

In accordance with Chapter 2, Article 4, Items VI, VII, and XII, the MAHs should designate a third level qualification health professional with technical capacity to be responsible for the pharmacovigilance of their products, and have a system for methodical, updated, and routine registration of activities and information related to the adverse event notifications received. They should also implement pharmacovigilance self-inspection actions, among other activities.

In general, Good Pharmacovigilance Practices are designed to guarantee:

- Authenticity of the data on drug-related risks collected for evaluation;
- Confidentiality of the information related to the identity of the persons, products, and institutions under the health surveillance process;
- Use of uniform criteria so MAHs and Health Authorities may evaluate the reports and promote a better perspective of safety sign identification.

1.3 Roles and Responsibilities of the Marketing Authorization Holder (MAH) and the Qualified Person Responsible for Pharmacovigilance (QPPV)

The Marketing Authorization Holder should ensure that he has an appropriate system of pharmacovigilance in place in order to meet the legal aspects of RDC no. 04/2009, and to ensure that appropriate action may be taken when necessary. The MAH should therefore ensure that all information relevant to the risk-benefit balance of a medicinal product is reported to the Brazilian Health Surveillance Agency (Anvisa) in accordance with the legislation.

The MAH is responsible for keeping a document that describes its pharmacovigilance system, as well as proof that the Qualified Person Responsible for Pharmacovigilance is technically qualified for his or her job.

The role of the QPPV is very important, and this document therefore describes the role and responsibilities of the QPPV and also provides guidance for the Marketing Authorization Holder on how to adequately support the QPPV in pharmacovigilance actions.

The MAHs should appoint one QPPV responsible for overall pharmacovigilance for all their medicinal products.

The QPPV should provide his or her contact information. If available, inform 24-hour contact details, in case the Health Authorities need them.

1.3.1 The Responsibilities of the Qualified Person Responsible for Pharmacovigilance (QPPV)

The Qualified Person Responsible for Pharmacovigilance (QPPV) should:

- establish and maintain the MAH's pharmacovigilance system;
- have an overview of the safety profiles and emerging safety concerns in relation to potential or real risk to public health posed by the medicinal products for which the MAH holds authorizations;
- acting as the MAH's single contact point for the Health Authorities on a 24-hour basis.

The QPPV should be responsible for a system with structure and performance to ensure:

- that all information about adverse reactions which are reported to the MAH, and to medical representatives, is collected and collated;
- that the pharmacovigilance system meets regulatory directives and guidance;
- constant improvement of its system, by means of continuous evaluation and self-inspection in post-commercialization period;
- that any request from the Health Authorities for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions, as well as studies conducted.

The MAH's pharmacovigilance system should be developed observing all relevant safety aspects, including quality control and assurance procedures, standard operating procedures, database operations, contractual arrangements, compliance data (e.g. in relation to the quality, completeness and timeliness for expedited reporting and submission of Periodic Pharmacovigilance Reports), audit reports, self-inspection, and training of personnel in relation to pharmacovigilance.

1.3.2 Responsibilities of the MAH in Relation to the QPPV

The MAH should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the full development of pharmacovigilance activities.

In addition, the MAH should ensure that there is full documentation covering all procedures and activities of the QPPV and that mechanisms are in place to ensure that the QPPV may receive or seek all relevant information. The MAH should also implement mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information relating to the evaluation of the risk-benefit balance.

The QPPV should receive sufficient authority:

- to implement changes to the MAH's pharmacovigilance system in order to promote, maintain and improve compliance of regulatory requirements;
- to provide input into Pharmacovigilance Plans and Risk Minimization Plans;
- to contribute towards the preparation of regulatory action in response to emerging safety concerns (e.g. urgent safety restrictions, and the production of technical information publications, such as communication to Patients and Healthcare Professionals).

The MAH should plan for business contingency, (e.g. in case of non-availability of personnel, adverse reaction database failure, failure of other hardware or software with impact on electronic reporting and data analysis).

1.3.3 Contractual arrangements

The MAH may transfer any or all of the pharmacovigilance tasks and functions to another person(s) or organization, but the ultimate responsibility for the fulfillment of all pharmacovigilance obligations and the quality and integrity of this always

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resides with the MAH. In such cases, it is the responsibility of the MAH to provide detailed and clear documented contractual arrangements on what activities will be developed by third parties. This contract should include the possibility that the SNVS will inspect their activities, depending on the necessity and specificity.

In cases of contractual arrangements between MAHs, there should be a clear definition of the responsibilities regarding pharmacovigilance concerns. However, these arrangements should include measures to avoid the duplicate submission of Individual Case Safety Reports.

2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

2.1 Introduction

The rapid and effective identification and assessment of drug safety issues is dependent on early access to complete information. This is fundamental to both Regulatory Authorities' and Marketing Authorization Holders.

This Section sets out the framework for implementation of the monitoring of compliance with pharmacovigilance obligations and of pharmacovigilance inspections.

2.1.1 Roles of MAHs

The MAHs should ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility for their products on the market and to ensure that appropriate action can be taken, when necessary. This includes the MAH having at its disposal continuously an appropriately qualified person responsible for pharmacovigilance in Brazil.

2.1.2. Roles of the Health Authorities

The Health Authorities are responsible for ensuring the compliance with the legislation, particularly RDC 04/2009.

2.1.3 Detailed Description of the Pharmacovigilance System (DDPS)

Every MAH is required to have a detailed description of its pharmacovigilance system and, where appropriate, of its risk management system. This document should be kept by the MAH and should be handed to the Health Authorities whenever required.

2.2 Description of the Pharmacovigilance System

The elements of the DDPS, which gives an overview of key functions and elements of the MAH pharmacovigilance system, are as follows:

2.2.1 Location

The MAH pharmacovigilance system should be located in Brazil. Even if the elements and processes are developed in other countries, the existence of an operational capacity of monitoring and identifying problems related to their medicinal products at national level is necessary. Another important factor is the fact that the MAH QPPV must live in Brazil.

2.2.2 Elements

The following elements are necessary for developing the MAH's pharmacovigilance system. Any other elements to be developed should be specified and added to the descriptive document.

a) Qualified Person Responsible for Pharmacovigilance (QPPV)

The QPPV should reside in Brazil. Each MAH should send its registration data to its State Health Surveillance Secretariat, such as:

- full name;
- commercial address;
- telephone number.

Other information should be available if requested, e.g.:

- Summary Curriculum Vitae, with the key relevant information on the QPPV's main qualifications, training and experience in pharmacovigilance;
- A summary of the job description of the QPPV;
- A description of the back-up procedure to apply in the absence of the QPPV.

b) Organization

The MAH should present the organization of its pharmacovigilance system. All elements should be described. Brazilian and international partnerships should also be included in the system's description, as well as the relationship levels of each part of the pharmacovigilance system, without the need to mention names. Where there is a partnership involving a particular medicinal product, it should be indicated.

Flow diagrams and schemes are important for the description of the work process and the AE notification sources. Therefore, they should be applied whenever possible to describe the MAH pharmacovigilance system.

c) Documented procedures

An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The following list indicates topics that should usually be covered by these written procedures:

- The activities of the QPPV and the back-up procedure to apply in their absence;
- The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting to the Health Authorities;
- The process should ensure that reports from different sources are captured;
- The follow-up of reports without outcome;
- Detection of duplicate reports;
- Production of Periodical Pharmacovigilance Reports;
- Description of pharmacovigilance activities, including:
 - Signal detection and review;
 - Risk-benefit assessment;
- Interaction between safety issues and product defects;
- Responses to regulatory authority requirements;
- Handling of urgent safety restrictions;
- Market launch of new products and their safety issues, e.g. execution of Pharmacovigilance Plan and Risk Minimization Plan;
- Management and use of databases and other electronic systems;
- Self-inspection (audits) and the inspection in the pharmacovigilance systems;
- Training;
- Filing.

These elements should be detailed in a written document and, when requested, they should be sent to the Health Authorities within five working days.

d) Databases

A listing of the main databases used for pharmacovigilance purposes and brief functional descriptions of these should be provided. If there is the need to transfer information to the SNVS among databases, this procedures should follow the regulatory rules.

e) Contractual Arrangements

Links with other organizations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities, in particular where the role of the QPPV, the reporting procedures, management of databases, signal detection, and the compilation of PPRs is subcontracted.

f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities. This also includes staff such as sales personnel or clinical research staff. Provide a description of the training system in the technical documentation of the pharmacovigilance system.

g) Quality Management System

The Pharmacovigilance System should have a quality management process as support. This includes the MAH roles and responsibilities, activities and documentation, quality control and system review, as well as corrective and preventive actions.

h) Supporting Documentation

The MAH should ensure that the pharmacovigilance system is in place and documented. Pharmacovigilance system related documents and information should be traceable by the MAH. Such traceability procedure may be evaluated in a pharmacovigilance inspection.

2.3 Monitoring of Compliance of Good Practices by the MAH

Set out below is an outline of how compliance monitoring should be performed by the Health Authorities. In this context compliance monitoring relates to activities that are separate to inspection activities and are carried out separately to them or as a prelude or follow-up to inspection. Thus, deficiencies identified during compliance monitoring may lead to an inspection request.

Competent authorities will ensure that a system of pharmacovigilance is in place within MAHs through scrutiny of ADR reports, MAH documentation, PPRs and through pharmacovigilance inspections.

2.3.1 Qualified Person Responsible for Pharmacovigilance

The MAHs should hand to their State Health Surveillance Secretariat the QPPV's contact data and any data update.

2.3.2 Change in the Evaluation of the Risk-Benefit Balance of a Product

One of the key responsibilities of Marketing Authorization Holders is to immediately notify the Competent Authorities of any change in the balance of risks and benefits of their products. Any failure to do so may pose a significant threat to public health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the Competent Authorities.

2.3.3 Expedited Adverse Reaction Reporting

Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 7 or 15 days after it is known, depending on the seriousness of the event) and submission of reports of poor quality (particularly where evidence suggests that this results from inadequate company follow-up of individual cases), and will result in consideration of enforcement action by the Competent Authorities.

Competent Authorities may use some methods for prospective monitoring of compliance with expedited reporting of adverse reactions:

- Monitoring adverse reaction reports received from Marketing Authorisation Holders against other sources that reported to both pharmaceutical companies and the health surveillance authorities;
- Absence of reports, with evidences of their existence;
- Monitoring the time between receipt by Marketing Authorization Holder and submission to Competent Authorities;
- Monitoring the quality of reports;
- Submission of reports judged to be of poor quality;
- Follow-up of reports sent electronically and assessment of the Periodical Pharmacovigilance Reports, noting discrepancies and underreporting;

At inspection there may be a review of a sample of reports to assess the quality of data, determine whether the relevant reports have been expedited and are included on the SNVS electronic system, and to confirm that procedures are complied with.

2.3.4 Periodical Pharmacovigilance Report

PPRs are important documents. They provide an opportunity for MAHs to obtain and maintain the marketing authorization for a medicinal product. Both MAH and Anvisa assess the safety profile of a product by means of this document. The MAH use this document to ensure that the Summary of Product Characteristics (SPC) and Package Leaflet are up to date. For these reasons, the Competent Authorities place great importance on compliance with periodic reporting.

Non-compliance may include:

- Non-submission: Complete non-submission of PPRs, submission outside the correct cycle, non-restart of the cycle of submission when necessary;
- Incorrect format of the document: Report not in accordance with RDC 04/2009, its guides and other legal provisions;
- Omission of information required by legal and regulatory provisions;
- Poor quality reports: Poor documentation of adverse reactions or insufficient information provided to perform a thorough assessment in the Presentation of Individual Case Histories section, new safety signals not or poorly assessed, or misuse not highlighted;
- Changes made to the DSRD, e.g. information leaflet, since the submission of the last PPR, with important distortions related to this PPR;

2.3.5 Information Requested by Competent Authorities

In principle, all information requests by the Competent Authorities to a MAH should be answered as soon as possible, within the established deadline. Undoubtedly, the

more urgent the pharmacovigilance related issue and its potential impact on the public health, the faster the answer to be sent should be. If the MAH does not meet the Competent Authorities' requirements within the established deadline, a deadline extension request should be sent, with a justification, for assessment. However, depending on the urgency, partial data may be sent first, until all necessary information is obtained later. If this occurs, this type of addressing should be described and duly justified for assessment by the Competent Authorities.

2.3.6 Provision of Additional Data on Studies

If there are new data from post-authorization studies, which indicate safety signs or changes to the benefit/ risk profile of medicinal products, the MAH should notify Anvisa as soon as possible.

2.4. Pharmacovigilance Inspections

To assess the compliance with pharmacovigilance regulatory obligations, the SNVS may conduct pharmacovigilance inspections. Inspections may be routine, to introduce a new medicinal product in the market, sporadic or even emergency inspections. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAH improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.

2.4.1 Conduct of Inspections

Inspections may be conducted by both Anvisa and State, Municipal, and Federal District health authorities. Thus, there should be collaboration and cooperation between Competent Authorities to minimize duplication and maximize coverage

2.4.2 Routine (Programmed) Inspections

Routine inspections are conducted by Anvisa and local Health Authorities. In general, a Brazilian inspection program is expected to meet the need of routine inspections. The focus of such inspections is to determine if the MAH have a PPR, systems and installations in Brazil in order to meet their health regulatory obligations. These inspections may be requested to assess one or more specific products, being used as concrete evidence of the MAH pharmacovigilance system operation.

The MAH will receive a communication on the programmed inspection with the agenda, which may contain a list of documents to be assessed.

Preference will be given to inspections based on the potential risk to public health, nature of products, level of utilization, and other risk factors.

2.4.3 Targeted inspections

Targeted inspections may arise when one or more of the following arise:

- The MAH has not previously been inspected;
- The MAH has placed a new product on the market or has recently been or is involved in a merger or takeover process, which may indicate the need to assess how the MAH's new pharmacovigilance system will be organized;
 - The MAH has changed their system significantly (e.g. new database system, contracting out of reporting activities).

Triggers for the inspection are identified which relate to specific concerns about a product's safety or actual non-compliance, e.g. significant issues relating to:

- Delays in carrying out or failure to carry out specific obligations;
- Failure to monitor product safety;
- Delays in expedited or incomplete reporting;
- Submission of poor quality or incomplete or inconsistent PPRs;
- Failure to communicate change in risk-benefit balance;
- Previous inspection experience;
- Information received from other authorities, including international ones;
- Poor follow-up to requests for information from the Competent Authorities;
- Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to Anvisa.

Despite the abovementioned examples being considered a potential concern, a targeted inspection will not always be conducted.

2.4.4 System inspections

These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations. They may use products as examples to test the system. This strategy may also be used in routine or targeted inspections.

2.4.5 Product specific inspections

These inspections focus specifically on a given product that generated a safety concern.

2.4.6 Inspections of Contractors and Licensing Partners

Any elements related to the MAH's pharmacovigilance activities may take part in inspection assessments. Regarding other companies that are part of the MAH's pharmacovigilance system, they may be inspected in order to confirm their capability to support the MAH's compliance with pharmacovigilance obligations. It is important to remember that the MAH is always the ultimate responsible for pharmacovigilance processes.

2.4.7 Unannounced Inspections

It is anticipated that the majority of inspections will be announced to the MAH. However, on occasions, it may be appropriate to conduct unannounced inspections.

2.4.8 Inspection reports and follow-up

Each inspection by the SNVS will result in a descriptive report, which should be made available to Anvisa, when requested. Where an inspection reveals non-compliance with regulatory requirements, the MAHs should prepare a remedial action plan to correct the non-compliances. If necessary, the MAH will be required to provide evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

2.4.9 Regulatory Action

The SNVS is obliged to implement health legislation. The application of sanction regulatory provisions will depend on the negative potential public health impact caused by the MAH, and on the non-compliance of regulatory requirements, particularly RDC no. 04/2009.

In addition to the provisions of Law 6437/77, the following action may result from the SNVS inspections:

- Guidance: recommendations on how to comply with the requirements;
- New Inspection: to determine the compliance with regulatory guidance or requirements;
- Warning: formal recommendations to the MAH on the need of correction or compliance with regulatory requirements;
- Urgent safety restriction: marketing or use suspension, or authorization cancellation regarding a given medicinal product.

References

VOLUME 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – PART I: Guidelines for Marketing Authorisation Holders, EMEA, September 2008.

GOOD PHARMACOVIGILANCE PRACTICES FOR THE AMERICAS. Draft 9, November 2008. Pan American Network on Drug Regulatory Harmonization. Working Group on Pharmacovigilance.